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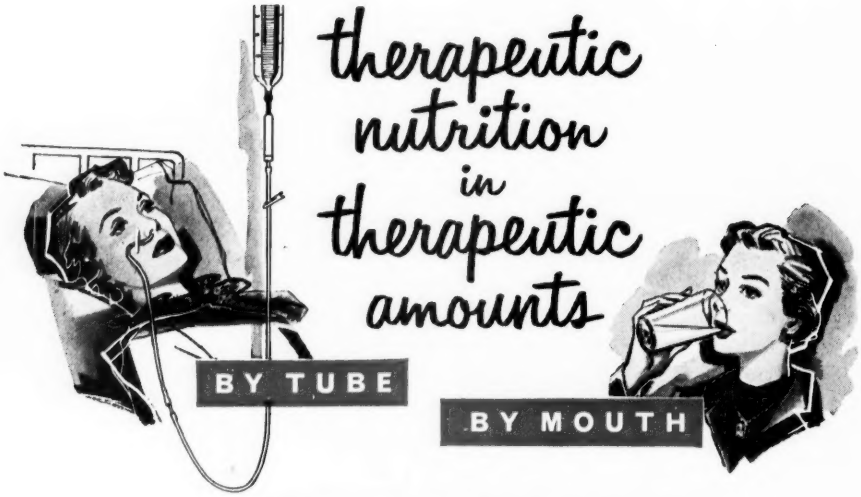

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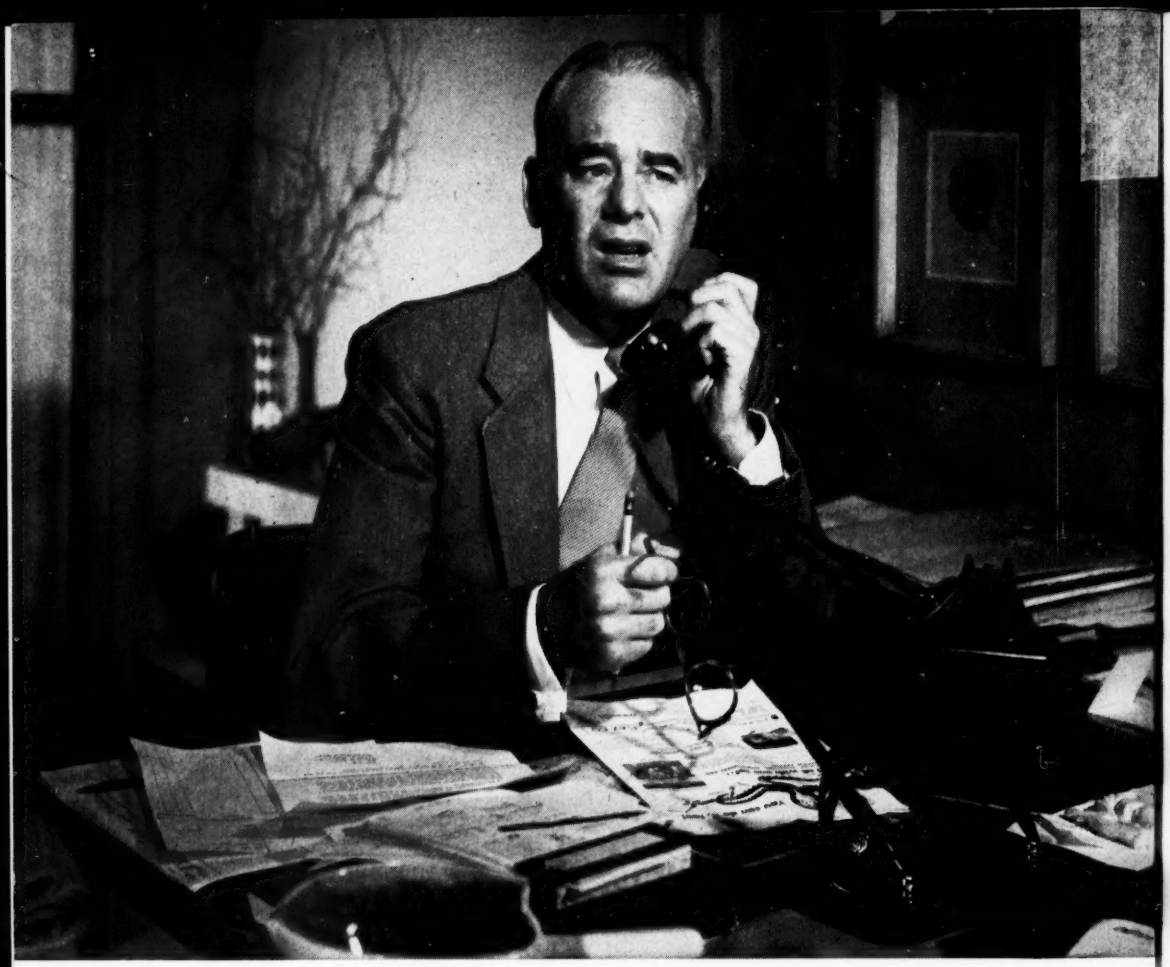

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SURGERY
GYNECOLOGY AND OBSTETRICS

VOLUME 99 SEPTEMBER, 1954 NUMBER 3

AN INTERIM REPORT UPON THE "SECOND LOOK" PROCEDURE FOR CANCER OF THE STOMACH, COLON, AND RECTUM AND FOR "LIMITED INTRAPERITONEAL CARCINOSIS"

OWEN H. WANGENSTEEN, M.D., F.A.C.S., F. JOHN LEWIS, M.D., F.A.C.S., STUART W. ARHELGER, M.D., JOHN J. MULLER, M.D., and LLOYD D. MACLEAN, M.D., Minneapolis, Minnesota

DESPITE the use of extensive primary operations for visceral cancers, there remains a large group of patients who are not cured by their initial procedure.

The systematic use of a second or even several exploratory operations following the original excision of a visceral cancer is a resolute effort to cure a higher proportion of the patients who have metastatic cancers. It is an experimental venture, not in accord with traditional views, which has generally been received with tolerant skepticism. Fortunately, some of our early experience with this new plan has been gratifying, and though the method cannot yet be recommended as a practical tool, we believe that it is worthy of attention and perhaps deserving of a trial by others. The concept has been briefly explained previously. Here we wish to describe the plan of treatment used, present the current status of the study, and discuss some of the difficulties that we have met in pursuing it.

From the Department of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota.
Supported by the Damon Runyon Fund for Cancer Research and the Minnesota Division of the American Cancer Society.
Dr. Muller, now at Roswell Park Memorial Hospital, Buffalo.

PLAN OF THE SECOND LOOK

Second look operations, as described here, are re-exploration operations done on patients who had gastric, colic, or rectal cancers with lymph node metastases. Approximately 6 months after the original excision and while they are still asymptomatic and have no clinical evidence of residual cancer, these patients are reoperated upon, and if possible, any residual cancer found is removed. If cancer is found at this second look operation, subsequent exploratory operations, called third or fourth looks, are carried out at similar intervals of time until no more cancer is found. Once a patient has undergone a negative exploration, no more surgery is recommended.

The details of this plan for doing re-entry operations are deserving of some further explanation. These details have been developed during the study as our total experience in doing secondary operations for cancer has increased, and in time they are certain to undergo further improvements and refinements.

For some time we have limited second look operations to patients with cancers already metastasized to the regional nodes at the time

of the primary operation. At the beginning of the study, reoperations were also used for asymptomatic patients who originally had large colic cancers adherent to adjacent structures but with no lymph node involvement, essentially large Dukes group B lesions. Residual cancer was found in none of these, however, and we have concluded that an aggressive primary resection is usually curative for for this type of cancer.

The patients whose cancers have metastasized to the regional lymph nodes or to sites away from the primary lesion offer a more challenging problem. They make up approximately two-thirds of any group with resectable visceral cancers, yet with conventional types of surgery, only a relatively small percentage are cured. The second look operation was designed especially for them.

It has been difficult to set the best interval of time to allow between operations. By the time the second look is done any residual local cancer should have grown large enough so that it can be detected by the surgeon but still be small enough so that it can be completely removed. Although approximately 6 months is given in the outlined plan as the suggested interval, some patients have had much longer intervals between their operations, up to 12 or 14 months, and still were found to have only small, resectable nodules of cancer when exploration was finally carried out. On the other hand, other, less fortunate individuals, have been found to harbor unresectable cancer even though they were explored after an interval of only 6 months. There is doubtless considerable variability in the rate at which residual cancer will grow large enough to produce symptoms, though in many patients, as Friesen and one of us (7) indicated, the "silent interval" is apt to be long—as long, in fact, as it often is before the primary tumor first causes symptoms. At any rate, there is no reliable way at present of deciding the best interval between operations for any individual patient. We have come to use somewhat shorter intervals for the patients with gastric cancer than for those with carcinoma of the colon, favoring an interval of slightly less than 6 months for the former and a somewhat longer interval, up to 8 months, for the latter.

Once the type of case to be treated and the period of time to elapse between operations have been chosen we are faced with another decision: when to stop reoperating. If it is possible to resect all the evident cancer at each operation we have continued to reoperate at intervals until a negative exploration (with negative histologic study of tissues removed) has been achieved. A total of 6 operations was done for 1 patient before the abdomen was free of cancer. The possibility of obtaining false negative explorations has been of concern. Conceivably false negatives could occur either by failure of the surgeon to recognize residual cancer or through the failure of the pathologist to find small areas of cancer in tissues removed. Accordingly, every effort has been made to do the reoperations thoroughly removing if possible all suspicious tissues. The specimens are identified and tabulated as to location and are meticulously examined, multiple histologic sections being used. In a study of 24 of the negative cases serial sections of the biopsy material averaging 2,151 sections per patient were examined to help eliminate errors arising from this source (5). It has been common to have as many as 30 specimens from a single case.

At the beginning a few patients who had cancer of the stomach or rectum were declared free of cancer after a second operation, but subsequently showed residual cancer.

In the colon group, however, no residual cancer has become evident in the group declared negative. It has been of great interest that thus far all of the patients who finally became free of cancer after having had residual cancer removed—the successfully treated patients—still show no evidence of residual cancer. In any case, it would appear that identification of residual cancer has been accurate.

CASE PRESENTATIONS

Perhaps the best way to elucidate the "second look" concept in cancer surgery is by presenting brief case summaries of 2 successfully treated patients. Both of these women had residual cancer at a second look operation but were finally free of cancer at some subsequent operation, and they still show no clinical evidence of cancer.

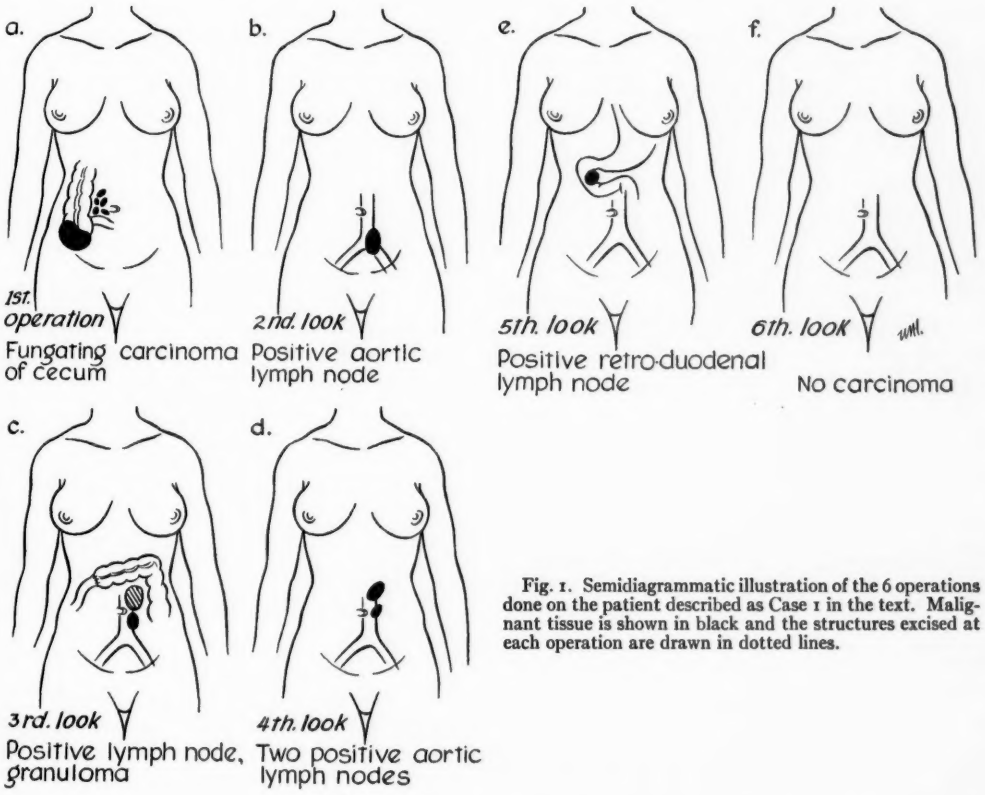

Fig. 1. Semidiagrammatic illustration of the 6 operations done on the patient described as Case 1 in the text. Malignant tissue is shown in black and the structures excised at each operation are drawn in dotted lines.

CASE 1. The clinical story of this woman illustrates a remarkable degree of courage, faith, and patience which is not uncommon among patients suffering from cancer and which needs to be more widely appreciated by members of the medical profession. It also, in retrospect, illustrates a measure of determination on the part of her surgeons for she was the first patient subjected to the second look program. Her case history has been presented in some detail previously (14).

This woman (Univ. Hosp. No. 797020) was 60 years old when first admitted to the hospital in October 1948 with an adenocarcinoma of the cecum which was excised with its lymphatic metastases on November first, as is shown in Figure 1a. While asymptomatic 5 months later she was readmitted and a second look operation was done. An enlarged lymph node, which proved on microscopic section to contain cancer, was removed (Fig. 1b).

She recovered rapidly from this operation and again had no complaints or clinical signs suggestive of residual cancer when her third look operation was done in July 1949. A large nodule was found in the transverse mesocolon and to remove it an additional segment of large and small bowel was excised, as is shown in Figure 1c. Though this large node proved on pathologic study to be merely a granuloma, one of the other lymph nodes from the periaortic region which was removed with it harbored malignant cells.

She returned again for a fourth operation 6 months after the third and had a fifth operation 9 months after the fourth. At each of these explorations metastatic cancer was found, as is shown in Figures 1d and 1e. At the fifth operation an extensive excision of the retroperitoneal tissues adjacent to the aorta and vena cava was done, a type of excision we now practice earlier in the course of this surgical program.

Even after this fifth operation her recuperative powers remained strong and her recovery was uncomplicated. With a level of hope perhaps not matched by that of her surgeons she returned to submit to a sixth and final operation after an interval of 5 months. This sixth look, which was done on February 19, 1951, was a careful general exploration with excision of a large amount of lymphatic-bearing tissue from the upper abdomen—the only areas in which lymph node excisions had not been done pre-

TABLE I.—REOPERATIONS ON 39 PATIENTS (50 OPERATIONS) FOR CANCER OF THE STOMACH

Status	No. of patients	Length of follow-up** after second look in months
No cancer found at second look, 17 patients		
Alive and well	13	Average 26 Range 1-40
Living with residual cancer	1	38
Dead of cancer	3	9, 8, and 17
Operative deaths	0	
Cancer found at second look, 22 patients (56 per cent)		
Alive and well, last look negative	1*	40
Alive and well, awaiting another look	3	0, 21†, 10‡
Living with residual cancer	4	0, 4, 10, 11
Dead of cancer	12	Average 7 Range 2-26
Operative deaths	2	——

*This patient has had 4 reoperations (summarized in the paper)
†Awaiting third look
‡Awaiting fourth look
**Length of follow-up has been computed in months from the second look to the time of the patient's last clinical examination.

viously. We were elated to find, after microscopic study, that none of this excised tissue contained residual cancer.

The patient has been examined frequently since her last operation and has shown no evidence of residual cancer. It is now 33 months since her sixth look and somewhat more than 5 years since the original operation was done.

CASE 2. This woman (Univ. Hosp. No. 816203) underwent 4 operations before she was finally free of a gastric cancer.

She was 55 years old when an obstructing cancer of the gastric antrum was excised on March 7, 1950. Because the cancer was adherent to the body of the pancreas and the mesocolon, as is illustrated in Figure 2a, all of the pancreas except the head as well as the mesocolon were removed with the stomach. Microscopic examination of the specimen indicated that the pancreas was actually not invaded with cancer though several lymph nodes were.

On this basis she was a candidate for a second look operation, so 4 months after the first operation her abdomen was explored. At this time she had no symptoms or clinical evidence suggestive of residual cancer, yet a grossly and microscopically involved lymph node adherent to the hepatic artery was found and excised (Fig. 2b).

Her recovery from this operation was rapid and she was apparently in good health when readmitted for a third look operation 6 months after the second. This time further metastatic cancer was found in 2 lymph nodes, one located near the hepatic artery and the other adherent to the upper part of the celiac axis, as is shown in Figure 2c. During the excision of these nodes the hepatic artery was injured and the cystic artery was divided, hence, to avoid gangrene of the gallbladder, a cholecystectomy was done. Though there was no apparent cancerous involvement, the spleen and splenic pedicle were also excised at this operation, a procedure we now do routinely at the original excision for all cancers of the stomach.

She returned for 1 more operation, her fourth, after an interval of 4 months. Again a careful search was made throughout the abdomen but the only tissue suggestive of metastatic cancer that could be found was a firm nodule adherent to the celiac axis. Since this nodule could not be separated from the vessel, the remaining celiac axis, including the common hepatic artery, was resected with it. After this, the remaining areolar tissue in the upper abdomen, adjacent to the aorta, portal vein, and vena cava was carefully removed (Fig. 2d). The patient was apparently not harmed by division of the hepatic artery which may mean that the gastroduodenal artery remained, though this possibility was not established by identification at the time of surgery.

Despite a painstaking, pathologic search, including examination of serial sections of the scarred nodule taken with the celiac axis, no cancer was found in any of the excised tissues. This patient is well and apparently free of cancer 31 months after the last operation and 45 months following the original gastric resection.

RESULTS

One hundred and three patients with lymph node positive cancers of the stomach, rectum, or colon have had second look operations. Further exploratory operations, after the second look, were done on many of them so that they have undergone a total of 141 operations following their original excisions. There were 6 operative deaths giving a patient morality rate of 5.8 per cent or an operative mortality rate of 4.3 per cent. The procedure does not seem to be unduly hazardous especially when it is pointed out that these operations are often difficult and long, even when no cancer is found; and if cancer is discovered, multiple bowel resections, in addition to a wide retroperitoneal excision, and a partial liver resection may be undertaken in an individual patient. With the techniques and supports of modern surgery, patients whose average age in this group was 65.5 years usually can be safely brought through a course of repeated extensive abdominal operations.

Of course this accomplishment is only important if it leads to attainment of the crucial

objective, that of curing patients who would otherwise succumb to their cancers. It can surprise no one to find that we still do not know if this end can be reached, for the patients have all had their second look operations less than 5 years ago. Nonetheless, there has been enough interest expressed in this concept of treatment such that a current summary report on all the patients treated so far seems justified.

Cancer of the stomach. Of the 39 patients, summarized in Table I, who originally had cancer of the stomach metastasized to the regional lymph nodes 17 were found free of cancer at the second look and 22, 56 per cent, were found to have residual cancer. Four of these 22 who had residual cancer are still alive and apparently free of disease. Two of them had only a second look and now await their third look, 1 patient has had three looks and awaits his fourth operation, while the other patient, described previously as Case 2, was free of cancer at her fourth look operation done 31 months ago.

Highly favorable conclusions cannot be drawn from the results we have obtained so far in this group, yet even one possible success among patients with a disease as fatal as residual cancer of the stomach has been encouraging. We are continuing to employ and are striving to improve the use of the second look for these patients but it has been difficult to settle upon potentially valuable changes in technique.

The same anatomic barriers that limit the extent of primary resections for this cancer are formidable obstacles during a second look operation. The major vessels and the head of the pancreas regularly restrict the extent of the excision, and these anatomic restrictions may, in fact, bear a greater influence on the poorer prognosis of operable cases when compared to colic cancers, for example, than any intrinsic or biologic differences between these malignant tumors. Certainly for all of the colon except the rectum a wide removal of the lymph drainage areas is more easily accomplished.

Though the problems are greater than in cancer of the colon, similarly wide excisions must be striven for in cancer of the stomach,

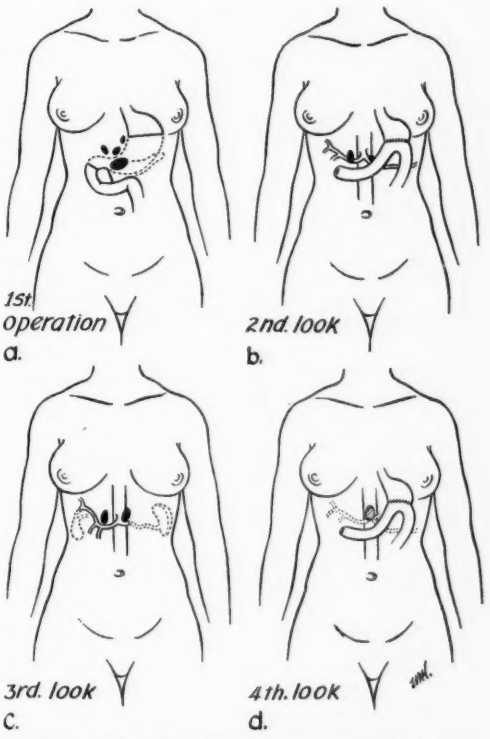

Fig. 2. The 4 operations done on the patient whose history is described as Case 2. Cancer was found at the first 3 operations but not at the last exploration.

and to this end we have increased the scope of the lymphatic removal routinely employed at the primary operation (Fig. 3). Excision of the greater and lesser omenta together with removal of the nodes around the abdominal esophagus have long been an essential part of a gastric resection for cancer. Since 1950 a splenectomy, together with excision of the splenic pedicle and the lymph node bearing tissues along the superior border of the pancreas have been practiced regularly during the gastric resection for cancer in this clinic (10, 12). Similarly, the celiac axis, the hepatic artery and the crura of the diaphragm as well as the adjacent aorta have been carefully freed of lymphatic tissue at the primary operation. Only recently have we extended this dissection in cleaning the hepatic artery to include the common bile duct and other structures of the

TABLE II.—REOPERATIONS ON 35 PATIENTS (46 OPERATIONS) FOR CANCER OF THE RECTUM

Status	No. of patients	Length of follow-up after second look in months
No cancer found at second look, 20 patients		
Alive and well	13	Average 19 Range 1-47
Living with residual cancer	5	44, 21, 22, 32*, 14*
Dead of cancer	2	2, 11
Operative deaths	0	—
Cancer found at second look, 15 patients (43 per cent)		
Alive and well, last look negative	1†	12
Alive and well awaiting another look	1	9
Living with residual cancer	1	6
Dead of cancer	11	Average 11 Range 3-33
Operative deaths	1	—

*Perineal pain is the only clinical evidence of recurrence.
†Though residual cancer was found at the second look, none was present at the third look.

TABLE III.—REOPERATIONS ON 29 PATIENTS (45 OPERATIONS) FOR CANCER OF THE COLON

Status	No. of patients	Length of follow-up after second look in months
No cancer found at second look, 15 patients		
Alive and well	15	Average 23 Range 2-46
Living with residual cancer	0	—
Dead of cancer	0	—
Operative deaths	0	—
Cancer found at second look, 14 patients (48 per cent)		
Alive and well, last look negative	4*	43, 50, 18, 50
Alive and well, awaiting another look	0	—
Living with residual cancer	1	5
Dead of cancer	6	Average 14 Range (8-22)
Operative deaths	3	

*Though these 4 patients had residual cancer at the second look operations, they were finally free of cancer after multiple operations, 3 at the third look and 1 at the sixth look

gastroduodenal ligament, the lymph nodes of the cystic artery, and cystic duct area as well as the lymph nodes along the vena cava beneath the second portion of the duodenum. Adjacent viscera are excised when involved by direct extension. When some cancer is left after such a primary procedure, it is to be found usually at a second look operation, located in areas where effective removal is difficult. It may be adherent to the aorta or the vena cava, or hidden within the porta hepatis, or placed deep behind the head of the pancreas, or it may have metastasized to the liver. Methods for removing these troublesome residuals completely are worth seeking for, and in some cases they may be the only cancer which remains.

Cancer of the rectum. In this group there has also been 1 patient who has apparently been successfully treated. Though residual cancer was found in 2 lymph nodes at a second look operation 6 months after a combined abdominoperineal resection of the rectum, no cancer was detected at a third look operation 11 months later. It has now been 21 months since her first operation but only 4 months since the negative third look.

Except for this patient, the results, as shown in Table II, have been poor, much poorer than those we have achieved in cancer of the colon. Here again the anatomic features are of vital importance. Residual cancer deep in the pelvis or on the perineal floor may, at the time of the second look operation, exist as diffuse, thin, plate-like areas which are difficult to recognize because they may be mistaken for scar. It is apparent now that cancer of this nature was missed in some of the earlier cases. More recently our skill in recognizing pelvic residual cancer has increased but satisfactory removal may still be impossible. In order to facilitate identification and allow a wide excision, if cancer is found, for some time we have approached the pelvis, as is routinely done at the primary excision, by simultaneous use of abdominal and perineal avenues with the patient in the lithotomy position. It remains to be seen whether this change in technique will lead to an improvement in the results.

Residual tumor found in retroperitoneal lymph nodes along the aorta and vena cava can be removed more easily. This is the type of residual cancer which is often found during second look operations for cancer of the colon, though in the colon cases, such residual cancer is not found in the concavity of the true pelvis. An extensive excision of the retroperitoneal

tissues adjacent to the great vessels and laterally on either side out to the ureters usually results in an adequate removal of the diseased nodes. If residual cancer were only located here, a high proportion of good results could be obtained, as has been the case among patients with cancer of the colon.

Cancer of the colon. Here, we come to the most effectively treated group. The second look procedure has brought about a heartening yield among patients with carcinoma of the colon. As is shown in Table III, there were 4 patients of the 15 found with residual cancer at the second look operation who were finally free of cancer at some subsequent operation. In each of these 4 patients the residual cancer was found in the secondary chain of retroperitoneal lymph nodes. One of these is the patient described before who had 6 operations. Though cancer was found at the first 5, none was found at the last operation, and she remains free of cancer more than 5 years following her first operation and 33 months after the last. The other 3 patients each had residual cancer at the second look operation but none was found at the third look. They all remain clinically free of cancer. Two have been followed for 56 months since the first operation; one of these has gone 40 months and the other 43 months since the negative third look operation was done. The fourth patient had his first operation 24 months ago and the third look 15 months ago. Further explorations are not planned for any of these 4.[1]

Fifteen patients, who originally had metastatic colic cancer, were free of cancer at the second look. It has been gratifying to find that all of these remain alive and well with no clinical evidence of residual cancer. For colic cancers, at least, the second look may prove to be accurate, and additionally it may have valuable prognostic significance. It would appear that patients with colic cancer who have had a negative second look can be assured of a favorable outlook.

[1]Since this paper was submitted for publication a fifth patient has been found to be free of cancer at the time of a third look operation. The 4 patients reported above have now been followed 41, 48, 51, and 24 months respectively since their negative look procedures. Thus 5 of 16 patients (31.2 per cent) with colic cancer having positive lymph nodes have become cancer-free through the agency of the second look procedure (July 28, 1954).

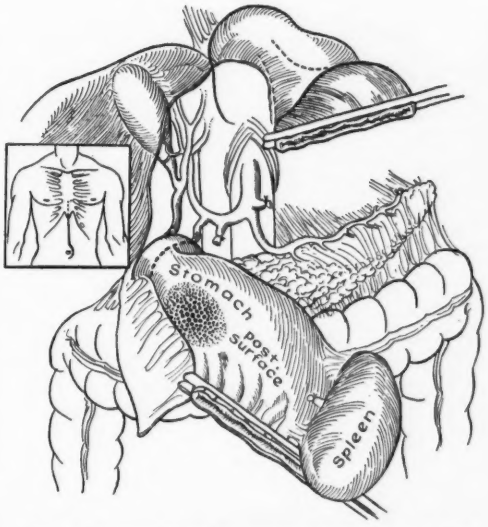

Fig. 3. Primary operation, cancer of the stomach: subtotal or total removal of the stomach, excision of the greater and lesser omenta, excision of the paraesophageal and retroduodenal lymph nodes, spleen, splenic pedicle, and lymph nodes along superior border of the pancreas. Radical dissection of lymphatic tissue from aorta, celiac axis, hepatic artery, and porta hepatis structures, including the lymph nodes adjacent to the cystic artery and gallbladder.

In this group too, there have been developments in the technique of performing a second look operation which may lead to better results. The extensive abdominoperineal excision mentioned under rectal cancer, is such a development.

REOPERATION FOR "LIMITED CARCINOSIS"

Included under the heading "second look" are only those patients who are free of clinical and x-ray evidence of recurrent or residual cancer prior to reoperation. However, the principle of multiple operations has been frequently applied to patients with known advanced intra-abdominal cancer not completely removed at an exploratory operation and patients who present obvious widespread residual cancer either on clinical or x-ray examination at the time of evaluation for reoperation (13). For clarity, these cases could be termed "limited abdominal carcinosis." Experience has taught that the ultimate cure of such cases is uncommon even when multiple resections of residual cancer are carried out. How-

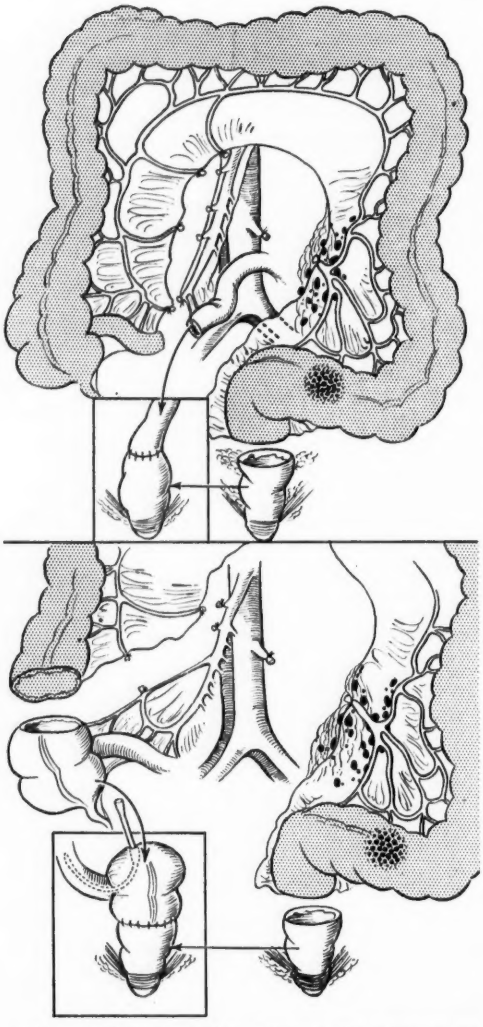

Fig. 4. Primary operation, cancer of the colon: 95 per cent removal of the colon, excision of the greater omentum, radical dissection of the aortic, vena caval, and upper iliac lymph nodes.

ever, some success in cases of this type has occurred, and although these operations are not truly second look procedures it seems not amiss to illustrate briefly this somewhat unorthodox use of surgery as a suppressive measure in the control of peritoneal carcinosis.

CASE 1. A 62 year old woman (Univ. Hosp. No. 824079) had a cancer of the sigmoid colon resected in December of 1949 at another hospital. She developed a large intra-abdominal mass and at reoperation in November 1950 there was widespread cancer within the peritoneal cavity. She was transferred to the University of Minnesota Hospitals and operated upon again in January of 1951. At this procedure it was possible to resect a large mass of residual cancer from the pelvis plus separate areas of spread to the transverse mesocolon, omentum, and ileum. She became asymptomatic and in June of 1951 re-exploration revealed residual cancer on the posterior wall of the bladder. A partial cystectomy was performed. In December 1951 residual carcinoma, now evident in the hepatic flexure of the colon, and an area of residual cancer over the sacrum were removed. In August 1952 a residual area of cancer in the transverse mesocolon was excised. On April 10, 1953 at a thorough exploration removing 22 specimens for histologic study, she was found free of recognizable carcinoma. She appears healthy and is apparently free of cancer 11 months later.[1]

CASE 2. This second patient with "carcinosis" (Univ. Hosp. No. 846845) is a 57 year old woman who had a huge carcinoma of the descending colon with extension and perforation to parietal peritoneum and abdominal wall forming an abscess, the walls of which were partially composed of cancerous tissue. In the wall of the colon away from the primary mass were several carcinomatous implants and there were implants in the mesentery of the colon in fat but no definite metastases to lymph nodes.

In July 1952 a resection of all visible cancer was carried out with removal of the entire colon (save a small portion of the cecum), the abdominal wall, and abscess en bloc and anastomosis of the cecum to the rectum. At a second operation in February 1953 excision of residual cancer in the abdominal wall was carried out, and at a third operation in August 1953 residual cancer in the left perirenal fat was removed. A recent re-exploration on February 11, 1954 with removal of many scarred areas for biopsy was negative.

CASE 3. This 48 year old woman (Univ. Hosp. No. 847145) had intra-abdominal carcinosis from a primary papillary cystadenocarcinoma of the ovary. There was extension to the opposite ovary, uterus, bladder, both ureters, sigmoid colon, and pelvic peritoneum. At the time of her primary operation in August of 1952 an en bloc resection of the carcinoma and its metastases was carried out consisting of removal of both ovaries, fallopian tubes, the uterus, lower portion of both ureters, a portion of the bladder, and the sigmoid colon. Reconstruction consisted of anastomosis of both ureters to the remaining bladder and of the descending colon to the rectum. Because of the extensive character of her primary tumor a second exploratory operation was carried out in February 1953. At this procedure thorough exploration with multiple biopsies of questionable areas revealed no residual. A nonfunctioning left

[1] A more recent exploration, however, disclosed the presence of cancer on the sacrum.

kidney was removed. It seemed unlikely that the widespread local dissemination of the carcinoma of the ovary observed at the time of the first laparotomy could have been completely controlled. Therefore, a third operation was recommended and carried out in November of 1953. It was gratifying to demonstrate again at this third procedure absence of residual of this extensive cancer. The patient has remained well.

These cases are interesting illustrations of the possible success of radical multiple operations in controlling what appeared to be almost hopeless situations. It is possible that there may be an application of similar en bloc resection techniques (Case 3) of removing the pelvic viscera including the ureters and sigmoid colon in selected cases of extensive cancer of the corpus and cervix uteri.

DISCUSSION

Resectable residual cancer. Obviously, sufficient time has not yet passed to establish or disprove our assumption that residual, abdominal cancers may often be completely resected. Yet, our early experience, expecially with cancer of the colon, suggests that this may be possible at least for some types of residual cancer. In all the satisfactorily treated "second look" patients the residual cancer has been located in only one or a few lymph nodes and limited to one area of the abdomen. For patients with this type of residual cancer the second look procedure may prove to be a crucial addition to the therapy.

In all cases an aggressive attempt has been made if the cancer appeared to be technically resectable even though it was located in several areas. However, liver metastases found at second look operations have so far not been completely ablated. Liver resections have been done at re-entry operations in 9 patients, yet all but 1 of these individuals are now dead or have developed inoperable recurrences. Many of these liver resections for metastatic cancer were done in a timid manner; they were simply enucleations of one or two metastatic nodules. Perhaps help may be given even to these patients if wider liver resections which are now possible are employed. A determined attack against the relatively advanced lesions has not been abandoned.

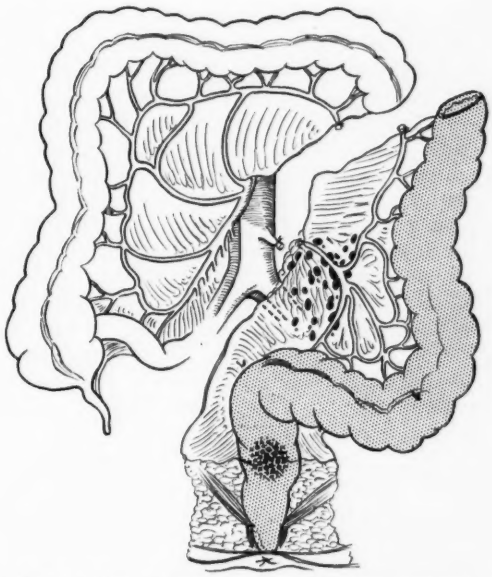

Fig. 5. Primary operation, cancer of rectum: combined abdominoperineal resection with removal of left colon and radical iliac, aortic, and vena cava lymph node dissection.

Extent of the primary operation. It might seem that routine use of the second look operation would incline the surgeon to count too much on this second chance and thus limit the extent of the original excision. In our experience, it has had the opposite effect. Since the "second look" procedure has been used in this clinic and we have been able to observe the location of residual cancer, more radical primary operations which increase the scope of the lymphatic excision have been employed for all visceral cancers. As previously described, an attempt has been made to accomplish a more complete removal of the lymphatic drainage in gastric cancers. Significant changes have been made also in the technique of removing colic and rectal cancers. For cancers of the colon beyond the hepatic flexure there has been a tendency in this clinic to resect the entire colon, thereby removing more of the regional lymph nodes as well as additional, undetected polyps, and cancers (4, 10). In these cases the distal ileum or a very small segment of cecum (in order to preserve the ileocecal valve function) is anastomosed to the

iliac colon or rectum (Fig. 4). A thorough dissection of the lymph channels and lymph nodes along the aorta and vena cava and similar dissection of the nodes of the common iliac vessels are carried out (Fig. 4). Most patients with cancer of the rectum have had the inferior mesenteric artery divided at the aorta with resection of the entire left colon and in some cases the distal one-half of the transverse colon as well, as described by State. During the past 2 years the iliac, aortic, and vena cava dissection has also become a more regular part of the primary "curative" operations for cancer of the rectum (Fig. 5). These radical operations, rather than more limited primary excision, follow as a logical consequence of the second look study.

It is improbable, however, that radical primary operations, even if carried further than they are at present, will eliminate the need for a second look operation. Of course it is to be granted that there would be no reason for doing a second operation if all the tissues, now removed only at the second operation, were excised at the primary operation. In practice this may not be possible, for metastases to nodes beyond the first barrier of regional nodes are sufficiently unpredictable that routine removal of certain areas would still leave other involved nodes to be detected only at a second operation. More radical primary operations, therefore, may actually extend the usefulness of second look operations.

The second look operation for other cancers. Attention in this report has been directed exclusively to cancers of the stomach, colon, and rectum, but the second look can be used for other malignant lesions with equal justification. There have not been enough of the less common visceral cancers treated with the second look as yet to justify a review of our experience but it has been used for patients with hypernephroma, carcinoma of the ovary, and fibrosarcoma. It may be of value in treating these and in treating other visceral cancers such as carcinoma of the small bowel as well. The principle has been applied also in treating carcinoma of the breast and it could be used similarly for other nonvisceral cancers.

Attitude of the patients. It is obvious in order to pursue a program such as this, that the individual patient must have a fairly complete understanding of his condition. He must know that he has had a cancer and he must be told the reasons for recommending a second operation. The risks involved and the fact that he may not be helped must also be explained. All this is accepted surprisingly well. And most patients who are advised to have second look procedures are willing to undergo repeated operations without urging from the staff. A frank explanation is essential here and it is generally best for all cancer patients.

As would be expected the cost of hospitalization has been one of the chief concerns of most patients who have undergone repeated operations. A pilot study such as this one has been possible only through the aid of research grants from the Damon Runyon Fund and the Minnesota Division of the American Cancer Society.

For the management of cancer by multiple operations to be available beyond the limited programs of research, some solution to this problem must be sought. There is an increasing tendency by the public to include visceral cancer among the "disaster diseases" with poliomyelitis and tuberculosis. Possibly resources from the patient, cancer organizations and social agencies, hospitals, and the medical profession will need to be combined to meet this need. Certainly the patients' appeals for help must continue to be answered, and therapeutic means such as the second look, admittedly expensive but offering hope, will gain increasing availability.

A proper perspective. Other than those actually afflicted with cancer, no group can hope more fervently for something better than surgery with which to treat disease than surgeons themselves. A more powerful tool is badly needed. Yet for most visceral cancers there is, at present, nothing else to use, and there may be nothing better for sometime. We must not, therefore, beguile ourselves into a period of standstill while trustfully waiting for the simple and miraculous solution. It is far wiser to explore diligently every reasonable way by which our present most effective treatment, surgery, may be put to wider use. Clinical experimentation guided by imaginative thinking and consistent with sound knowledge

of pathology is justified and, in fact, is essential if the results of surgical treatment are to be improved upon.

The second look is such a clinical experiment. We cannot at present recommend its general acceptance but only suggest that an open frame of mind be used in its scrutiny and that the tentative success so far achieved in a few patients be measured against the utter hopelessness of recurrent cancer in the past.

SUMMARY

The second look in cancer surgery is a new concept employing systematic reoperations to remove asymptomatic, residual cancer. It has been used for 103 patients with cancers of the stomach, rectum, or colon in which there were metastases to the regional lymph nodes at the original excision. The plan has been to perform a second operation a few months, 6 to 8 usually, after the first while the patients still showed no clinical evidence of residual cancer. Any residual cancer found was excised if possible and then additional operations were done at intervals of approximately 6 months until one operation was completed at which no more cancer was found.

Six patients who had residual cancer at the second operation have finally been found free of cancer at some subsequent operation. They are still alive without evidence of residual cancer. One of the 6 patients had cancer of the stomach, 1 had cancer of the rectum, and 4 had cancer of the colon. The second look procedure would appear to exhibit greatest promise in patients with colic cancer.

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THE BEHAVIOR OF LOCAL FOCI CAUSING RECURRENT STREPTOCOCCAL INFECTIONS OF THE SKIN, SUBCUTANEOUS TISSUES, AND LYMPHATICS

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ERYSIPELAS has been called a notably recurrent disease. It recurs in about 20 per cent of patients in whom the same area is usually repeatedly infected. The behavior of the foci and the characteristics of the beta hemolytic streptococci isolated during attacks have been studied.

CLINICAL MATERIAL

Between 1931 and 1941 thirty-four patients with recurrent infections were under observation for periods of 2 to 4 years. In 13, streptococci were cultivated from foci or the tissues in 2 or more attacks. In 9 of these, the foci were superficial. In 4 of the 9, attacks occurred until active foci healed; in the other 5, the foci healed after each infection but were relighted coincident with each attack. In the other 4 of the 13 patients, the affected areas were edematous prior to initial invasion. In these the foci were occult; cultures were made of the deep tissues during acute exacerbations.

METHODS

The principal purposes of the cultures and serologic studies were to determine whether the same strain caused a patient's recurrent infections and if the strains were demonstrably different from other streptococci. The most suitable methods to accomplish these ends were utilized. All irrelevant data have been omitted from the report.

Cultures. All cultures were made on rabbit blood agar or in 2 per cent proteose peptone broth.

In culturing superficial foci or skin, the area was cleansed with acetone, the surface was denuded, and cultures were then made directly on blood agar plates. The areas were also scraped and the scrapings shaken in a small amount of saline solution which was subcultured on several Esmarch dishes layered with blood agar.

Deep tissue cultures were made in one of two ways. The skin was sterilized with acetone and punctured deeply at several points. The exuded material was put on plates. If the infection seemed deep a small amount of salt solution was injected, aspirated, and ejected onto semisolid media. Several punctures or injections were done. Positive cultures were obtained from the tissues in only 30 per cent of attacks. There were never more than a few colonies on these plates.

Colony characteristics. All the strains were diffusely hemolytic on rabbit blood agar. On this media the colonies were opaque or semiopaque. Two of the foci (Table I, LT and FT) harbored more than 1 strain. These strains were detected because the colonies were either more hemolytic or more granular than those of the strains found in previous cultures and were serologically different from the strains cultivated from the tissues.

Serologic methods. Agglutination was done on slides according to the method of Griffith.

In a previous study in which it was shown that strains in the throats of carriers were the same as those in postoperative wound infections (4, 6, 7) sera were prepared with both strains. These strains reciprocally agglutinated in and absorbed both sera. Sera were prepared with all of the strains isolated in cultures from attacks in patients in Tables I and III. Except to show that strains from different patients were seldom homologous no information was gained beyond that obtained with the serum of 1 of the strains. The complicated data from cross agglutinations have been omitted. Only reactions with 1 serum have been given in the tables.

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The sera were prepared by inoculating rabbits with heat killed, then living, streptococci. The sera were diluted 1 to 5. Five milliliters of this dilution were absorbed with four or five 100 milliliter lots of culture which had been heat killed, centrifuged, and drained of media. The bacteria used for agglutination in the diluted sera were grown 18 hours, washed, and resuspended in broth. If a strain completely absorbed the serum of another strain the 2 strains were considered homologous.

There were 26 cultures, 2 from each patient. Actually since the strains from the cultures of 9 patients were proved to be identical there were in all, 17 different strains. Of these, 13 were definitely typed, available sera failed to agglutinate 2, and the typing of another was questionable. One strain was not typed.

Toxin. Strains were grown in proteose peptone broth for 4 days. The cultures were filtered, diluted, and tested intradermally in patients with positive Dick reactions. All positive reactions were neutralized with scarlatinal convalescent sera. With some the neutralization was only partial. Of the 13 patients only 1 (MM, Table II) reacted positively to a standard intradermal testing dose of scarlatinal toxin.

CLINICAL AND SEROLOGIC DATA

The patients have been grouped according to the behavior of their foci.

Recurrent attacks caused by superficial persistent foci (Table I). Two of these patients had recurrent attacks of facial erysipelas and 2 had leg infections with an associated lymphangitis. The facial infections were caused by infected eczemas of the external ear and those of the legs by patches of interdigital dermatitis harboring streptococci. Attacks ceased when these foci healed.

In each patient identical strains of streptococci were recovered during 2 successive infections. The strains from the 4 patients were serologically heterologous. Strain LT was type 12 and RG, type 6. Strains from the other 2 patients were not typed. Of the 4 strains, FT and RG were strongly toxigenic.

The intervals between attacks in these patients varied from 1 to 6 months. Possibly these intervals indicate the duration of local tissue immunity to the strains in the respective patients. In those with aural eczema, extraneous strains were found in the foci in the intervals between the attacks. These strains were not recovered from the tissues. No fungi were found but the strains causing the infections were always present in the foci until healing occurred. The extraneous strains presumably acquired by contact were not the cause of the erysipelas.

Recurrent attacks caused by the reactivation of old foci (Table II). The foci in this group of patients healed between reinfections. Streptococci were never cultivated from scrapings of the skin at the healed sites. The intervals were longer than in patients (Table I) with unhealed foci which were a continuous source of infection. According to case histories not included in this report, years may elapse before foci are relighted; but even after these long intervals the sites of the previous infections, the same foci, and approximately the same areas of the skin and subcutaneous tissues have been invaded a second or third time.

In 1 patient (MM) the strains recovered from 2 successive infections were identical; in the others the strains were different. Of 5 strains from different attacks (MM_2, JG_3, MP_2, TS_3, and TS_4) 2 (TS_3 and JG_3) produced no demonstrable toxin. The Dick test was positive in only 1 patient (MM). The strains recovered from cultures of 6 attacks were typed; of these, 2 (MP_2 and JG_3) were homologous.

Apparently in this group of patients, after the initial infection, the reactions of the affected tissues have been modified in some manner so they have been more susceptible to invasion with streptococci. No bacteria were harbored at the sites, the intervals might be long, and successive attacks have been caused by heterologous strains. There is at present no entirely adequate explanation of the mechanism underlying these infections.

Latent foci in edematous tissues (Table III). In these patients edema preceded the initial infection. Two had congenital telangiectasis and 2 edema of an arm following mastectomy. While under observation there were no super-

TABLE I.—RECURRENCES FROM CHRONIC INFECTED FOCI

Patient	Age, years	Infection and focus	Attacks previous to observation	First attack cultured	Second attack cultured	Interval between cultures 1 and 2, mos.
LT	37	Aural eczema Face	4	Attack No. 5 Strain from focus LT_5	Attack No. 7 Strain from focus LT_7, tissue LT8	2
FT	12	Aural eczema Face	2	Attack No. 3 Strain from focus FT_3	Attack No. 4 Strain from tissue FT_4	4
RG	16	Interdigital dermatitis Leg	2	Attack No. 3 Strain from focus RG_3	Attack No. 4 Strain from focus RG_4	5
TM	29	Interdigital dermatitis Leg	3	Attack No. 4 Strain from focus TM_4	Attack No. 5 Strain from focus TM_5	6

Serologic Data

Pt. FT: Serum FT_4 agglutinated FT_3+++; absorbed by FT_3 completely.
Strains not agglutinated in available type sera.
Pt. LT: Serum LT_7 agglutinated LT_5++++, absorbed by LT_5 completely.
Strains LT_5, LT8, and LT_7, group A, type 12.
Pt. LT: Serum LT_7 agglutinated LT8+++; absorbed by LT8 completely.
Pt. RG: Serum RG_3 agglutinated RG_4+++; absorbed by RG_4 partially.
Strains RG_3 and RG_4, group A, type 6.
Pt. TM: Serum TM agglutinated TM++++; absorbed by TM almost complete.
Strains could not be typed with sera available.

TABLE II.—REINFECTIONS FROM RECURRENT FOCI

Patient	Age, years	Infection and focus	Attacks previous to observation	First attack cultured	Second attack cultured	Interval between cultures 1 and 2, mos.
MM	12	Dermatitis Infection of leg	1	Attack No. 2 Strain MM_2 from focus	Attack No. 3 Strain MM_3 from focus	12
TS	45	Ulcer, foot Infection of leg	2	Attack No. 3 Strain TS_3 from focus	Attack No. 4 Strain TS_4 from focus	12
JG	28	Paronychia Infection of arm	1	Attack No. 2 Strain JG_2 from tissue	Attack No. 3 Strain JG_3 from tissue	24
MP	35	Paronychia Infection of arm	1	Attack No. 2 Strain MP_2 from focus	Attack No. 3 Strain MP_3 from tissue	18
LR	17	Dermatitis Infection of leg	2	Attack No. 3 Strain LR_3	Attack No. 4 Strain LR_4	6

Serologic Data

Pt. MM: Serum MM_2 agglutinated MM_3++++; absorbed by MM_3 completely.
Strains not typed.
Pt. TS: Serum TS_4 agglutinated TS_3±; not absorbed by TS_3.
Strain TS_3, type 4; TS_4 not typed.
Pt. JG: Serum JG_2 agglutinated JG_3±; not absorbed by JG_3.
Strain JG_2 not typed; JG_3, type 4.
Pt. MP: Serum MP_2; no agglutination or absorption with MP_3.
Strain MP_2, type 3; MP_3, type 9?.
Pt. LR: Serum LR_3 agglutinated LR_4−; not absorbed by LR_4.
Strain LR_3, type 5; LR_4 not typed.

ficial foci which may have served as portals of entry. Although the strains from different patients were not the same, the same strain was found in both cultures from the tissues of the patients in successive attacks. The intervals between exacerbations of infection varied from 5 to 15 months.

Strains from 3 patients were typed. One was type 13, 1 was type 3, and 1 was indefinite. Of the 4 strains 3 produced weak scarlatinal toxins. Dick tests were negative on all 4 patients.

Since the identical strains were cultivated from the deep tissues in successive attacks and there were no apparent superficial foci or portals of entry, these strains probably lay quiescent between acute exacerbations.

DISCUSSION

Patients in the first group (Table I) had foci which behaved as anticipated. Strains harbored in them from time to time invaded adjacent tissues. Although the strains cultured from successive attacks in each patient were identical, those from different patients were heterologous. They had no demonstrable common characteristics to distinguish them from other strains from other sources.

Patients in the third group (Table III) had more interesting infections. Superficial foci

TABLE III.—RECURRENT STREPTOCOCCAL INFECTIONS OF LYMPHEDEMATOUS TISSUES

Patient	Age, years	Cause of edema	Focus	Attacks previous to observation	First attack cultured	Second attack cultured	Interval between cultures 1 and 2, mos.
JB	47	Arm Radical mastectomy	None reported or found	1	Attack No. 2 Strain JB_2 from tissue	Attack No. 4 Strain JB_4 from tissue	15
RR	41	Arm Radical mastectomy	None reported or found	2	Attack No. 3 Strain RR_3 from tissue	Attack No. 4 Strain RR_4 from tissue	5
RS	10	Arm Congenital lymphedema	None reported or found	1	Attack No. 2 Strain RS_2 from tissue	Attack No. 3 Strain RS_3 from tissue	11
TS	7	Leg Congenital lymphedema	None reported or found	2	Attack No. 3 Strain TS_3 from tissue	Attack No. 4 Strain TS_4 from tissue	12

Serologic Data

Pt. JB: Serum JB_4 agglutinated JB_2++++; absorbed by JB_2 completely. Strains JB_4 and JB_2, group A, type 13.

Pt. RR: Serum RR_3 agglutinated RR_4+++; absorbed by RR_4 completely. Strains RR_3 and RR_4, group A, type ?.

Pt. RS: Serum RS_3 agglutinated RS_2+++; absorbed by RS_2 partially. Strains RS_3 and RS_2, group A, type 3.

Pt. TS: Serum TS_4 agglutinated TS_3++++; absorbed by TS_3 completely. Strains not typed.

were never found. Recurrent streptococcal infections may cause local edema and fibrosis, but areas already edematous because of some congenital or acquired abnormality of lymph drainage are highly susceptible to spontaneous streptococcal infections. Drinker (1, 3) observed spontaneous infections of the extremities of dogs when the lymph channels had been obstructed. According to the histories of these patients, the initial infections were through occult foci. In none of the attacks were there demonstrable superficial foci or portals of entry. Of course, idiopathic infections similar to the initial infections may have occurred later but the attacks studied were apparently caused by strains which in the free intervals lay quiescent in the edematous tissues. In severe infections the inflammation has been practically continuous because attacks were so close together. Often staphylococcal infections have been superimposed on streptococcal infections.

The most interesting infections were those of patients in Table II, because, apparently, tissues once invaded with streptococci were highly susceptible to reinfection. So far we have no entirely adequate explanation of the tissue reaction responsible.

There are other recurrent infections which clinically resemble those we have described. Many localized infections of the respiratory tract are repeated according to patterns. After the initial infection, conjunctivitis, pharyngitis, blepharitis, sinusitis, otitis, laryngitis, and bronchitis tend to recur. After a few years these respiratory patterns may be erased. Unfortunately, investigation of these respiratory infections has been very difficult, and recently there have been few streptococcal infections to study. Occasionally staphylococci cause recurrent infections of the skin and subcutaneous tissues with foci which behave much like those of similar streptococcal infections. These infections have been studied (5).

One localized streptococcal infection of the upper respiratory tract, recurrent pharyngitis, has been studied intensively by many investigators because in rheumatic children a recurrence may provoke an attack of rheumatic fever. The course of these pharyngeal reinfections has been essentially similar to that of recurrent dermal infections. The tonsils and nasopharyngeal lymphadenoid tissues become chronically infected with streptococci. These foci may cause acute exacerbations of the chronic pharyngitis, but even after the foci have been surgically removed, the nasopharynx of these patients is especially susceptible to streptococcal reinfection. These reinfections of the nasopharynx have been prevented only by the continuous use of bacteriostatic or antibiotic drugs.

The clinician is never surprised if sinusitis, otitis media, or externa, pyelitis, or cystitis recur. The initial infection may complicate

some anatomic variation or local condition which has lowered the local resistance of the affected tissues or invasion may occur initially with an especially virulent bacterium. Subsequently, even though anomalies are corrected and infection overcome by appropriate therapy, there may be recurrences of these infections and frequently superimposed infections with other bacteria. Although the foci and infected tissues cannot be adequately cultured and the reactions to infection studied, the clinical course so closely resembles the course of recurrent dermal infections it is probable that the foci in all these infections behave similarly.

CONCLUSIONS

Local streptococcal infections repeated according to a pattern may be caused by adjacent foci harboring streptococci or, if the tissues are edematous, by strains which lie dormant in the affected tissues between attacks. Moreover, tissues which have once been infected are highly susceptible to subsequent invasion by strains of other types even after long free intervals. This susceptibility to reinfection accounts for many recurrences. The foci causing recurrent streptococcal pharyngitis behave like the foci in these dermal infections, and even after the foci have been surgically removed, the nasopharynx of a patient with one of these recurrent infections has been especially susceptible to subsequent attacks. Presumably the foci in other recurrent infections which cannot be satisfactorily studied behave like the foci in recurrent dermal infections.

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DIVERTICULUM OF THE FEMALE URETHRA: PROBLEMS IN DIAGNOSIS AND TREATMENT

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MANY interesting papers concerning diverticulum of the female urethra have been written in the past decade. Before that time this condition was a forgotten problem and one that was not recognized in many cases. I should like to call attention to certain points that have been found helpful at the Mayo Clinic in making the diagnosis of urethral diverticulum in the female. Suspicion of the presence of such a lesion can be aroused when a detailed history is obtained. Also, proper vaginal and urethroscopic examination becomes a necessity if many of these lesions are to be found. The object of this paper is to focus attention on these points and to present 4 illustrative case reports.

HISTORY

The symptoms usually recorded in case reports concerning diverticulum of the female urethra have been burning on urination, frequent urination, and dysuria. This triad may be encountered in almost any infection involving the urinary tract and these symptoms alone will not ordinarily arouse suspicion of a urethral diverticulum. Frequently, the patient may be aware of a mass protruding from the vagina just below the urethral orifice. Too often this is thought to be due to a relaxed perineum with an associated cystocele. If the mass is mentioned by the patient, the physician usually receives a strong hint that a diverticulum may be present. However, this condition is not excluded even if the patient does not complain of such a mass, as the bulge may be too far up on the anterior wall of the vagina to present externally.

A survey of records at the clinic shows that patients who have urethral diverticula usually complain more bitterly than do those who have simple granular or cicatricial urethritis. Frequency and burning may not be increased particularly but the accompanying urgency and especially dysuria often are extremely severe. Also, the duration of symptoms in many of these patients is exceedingly long. They may have had many periods of treatment with chemotherapeutic agents, local instillations and dilatations with only temporary relief. Patients often state that while they are voiding and after they finish they may experience a sense of fullness or pressure in the region of the urethra or anterior vaginal wall; it feels as though something is there which should be expelled. A number of patients state that if they insert a finger in the front part of the vagina and press upward they frequently can relieve themselves. This sense of fullness or pressure usually occurs when the diverticulum is of fairly good size; however, this discomfort may be noted with smaller pouches.

Still another point that often can be obtained in the history and that is related to the sac or pouch concerns the loss of a small amount of urine not long after voiding. Many times the orifice of the diverticulum is large enough to allow urine to enter the pouch during micturition; when this occurs, the patient occasionally may state that when she arises from the stool and walks away a small amount of urine comes away and soils her clothing. This results no doubt from the activity of the perineal muscles, which compress the sac and evacuate its contents.

Dyspareunia is another frequent symptom; at times it may be severe enough to prevent any attempt at intercourse. However, absence of this complaint does not mean that a diverticulum of the urethra is not present.

DIAGNOSIS

While a detailed history can be most helpful, the examining urologist must be aware of

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the rather difficult problems that may be confronted when an attempt is made to demonstrate the lesion during vaginal and endoscopic examination. The technique of vaginal examination should be modified to include massage of the anterior vaginal wall before the speculum is passed. Any swelling or pouching should be noted and the massage should consist of a stripping motion that should empty the diverticulum of its contents and force them out of the external meatus.

All urologists have seen a number of patients who have been examined repeatedly both gynecologically and urologically without the lesion being found. On more than one occasion, competent urologists have failed to find the orifice of the diverticulum during cystoscopic examination only to have the general physician find evidence of the lesion by proper examination of the vagina. I should like to suggest a possible cause for this error. The most commonly used endoscopic instruments employ the right-angle and foroblique lens systems. When these are used, the close proximity of the urethral mucosa to the lens precludes satisfactory examination of the urethra, particularly with the right-angle telescope. My colleagues and I have found that use of the panendoscope, with its straight-ahead view, or use of the direct-vision cystoscope becomes absolutely necessary to see the orifice that leads to the diverticulum being sought. These orifices in many instances are almost too small to be seen even with these useful instruments, and if the lesion is suspected it is always well to massage the anterior wall of the vagina while the cystoscope is in place and the urologist is watching closely. Many times the most insignificant little dimple in the floor of the urethra proves to be the entrance to a diverticulum. Pressure from the vaginal side allows expression of purulent material from the sac; this material is ejected into the urethral channel like tooth paste from a tube. The importance of vaginal pressure over the cystoscope when such a lesion is suspected always must be appreciated.

While the vast majority of urethral diverticula have their openings in the floor of the urethra, a small percentage will be found to open along the lateral walls, and in a few instances the orifice has been found on the anterior surface of the urethra.

Roentgenologic examination is frequently helpful in outlining the size of the pocket, in determining whether or not it is multilocular, as many of them are, and in disclosing whether or not stones are present. The latter complication occurs in a small percentage of cases. Malignant lesions also have been reported. The best way to outline a pocket is to attempt to coil a No. 4 opaque ureteral catheter in the pocket. After the catheter is softened in warm water, an attempt is made to insert its tip into the orifice of the diverticulum by means of a direct-vision cystoscope; the catheter then is gently twisted and passed farther at the same time so that it passes into the sac in a coil. Reontgenograms are then taken before and after injection of a small amount of opaque material. These procedures will demonstrate the size of the pocket and whether or not it is multilocular, a fact that should be known at the time of surgical repair.

At times it is impossible to insert a catheter into the diverticulum for even a short distance but this does not necessarily exclude the demonstration of the lesion by roentgenologic methods. Barnes and others have called attention to use of a specially prepared bag cathether that allows injection of contrast medium directly into the urethral channel. This has proved successful in outlining the pocket when it has been impossible to coil the catheter through the cystoscope. Still another procedure has been helpful in such instances. A glass syringe (asepto) is filled with the contrast medium and placed with its nozzle directly against the external meatus. The medium is then forced into the urethral cavity by compression of the bulb. All of these techniques may prove helpful in certain instances and one should be aware of their possibilities as aids in diagnosis.

Another clinical entity which may present a problem in differential diagnosis is duplication of the kidney in which the ureter of the upper segment has an ectopic opening in the urethra. Such an orifice may be suspected of being the opening into a simple urethral diverticulum. In some instances, surgical repair of the "suspected diverticulum" has been carried out

only to find that the patient then experiences other symptoms, namely either leakage from the vaginal wound where the repair was attempted or symptoms referable to the affected kidney because of the closure of the lower end of the ectopic ureter.

The following cases serve to emphasize the afore-mentioned points.

REPORT OF CASES

CASE 1. A 43 year old white woman registered at the clinic in September, 1952. Since 1940, she had passed blood in her urine on numerous occasions but had not consulted a physician until 1950, when a competent urologist had diagnosed a stricture of the urethra. A series of dilatations was given, after which she had noted no further hematuria. At the time of registration at the clinic her symptoms consisted largely of suprapubic soreness with a frequent urge to urinate; however, attempts at voiding resulted in the passage of little or no urine. The urine repeatedly had shown evidence of infection. Intermittent chemotherapy with dilatation of the urethra had been carried out for more than a year without improvement.

Physical examination revealed no definite abnormalities. Palpation of the urethral region disclosed nothing unusual. Urinalysis showed a mild degree of pyuria; cultures of the urine showed no growth of organisms. Cystoscopy revealed a 2 millimeter orifice exuding purulent material in the midportion of the urethra just left of the midline. A catheter was passed into the pocket, and a roentgenogram demonstrated a urethral diverticulum. This was removed surgically through a vaginal approach.

CASE 2. A 40 year old white woman registered at the clinic in May, 1952. An aching sensation in the urethra had been present for 4 months, associated with urgency requiring passage of urine. After each voiding, she had the sensation of wanting to pass more urine. She had to urinate 10 times daily but only occasionally at night. At times the aching increased in severity and would last through a period of 2 or 3 days. Previous treatment had consisted of use of urinary antiseptics but had been without benefit.

Physical examination disclosed no significant abnormalities. Examination of voided urine disclosed a moderate number of erythrocytes and pus cells. Cultures of the urine produced no organisms. Catheterized urine contained only a few pus cells. Cystoscopy revealed a 2 millimeter orifice at the 3 o'clock position in the midportion of the urethra. It was possible to coil a No. 4 ureteral catheter into this orifice. A necrotic diverticulum approximately 1 inch (2.5 cm.) in length was removed surgically through the vaginal route.

CASE 3. A 44 year old white woman registered at the clinic in January, 1952. She had had considerable difficulty for approximately 10 years, manifested by burning, frequency, urgency, stress incontinence, and a feeling of incomplete emptying of the bladder. She stated that a vaginal hysterectomy and repair of a ureterocele and cystocele had been done in October, 1951. The referring urologist, in December 1951, had noticed extensive scarring of the floor of the urethra, with thick purulent secretion appearing at the urethral meatus on withdrawal of the cystoscope. Further cystoscopic examination at that time and again just before her visit to the clinic failed to reveal any unusual orifices. Massage of the anterior vaginal wall always produced purulent secretion at the meatus.

An excretory urogram that she brought with her disclosed nothing unusual. Cystoscopy at the clinic showed extensive scarring of the floor of the urethra with considerable inflammation. Numerous openings were noted in the floor to the left of the midline. One of these was catheterized with a No. 4 opaque ureteral catheter. Roentgenograms demonstrated a diverticulum.

Surgical excision of the urethral diverticulum was done. Except for occasional slight burning and frequency, she has had little trouble since. All symptoms have been greatly reduced. A follow-up examination in December, 1952, showed minimal cicatricial and granular postoperative changes.

CASE 4. A 37 year old white woman registered at the clinic in October, 1952, because of vaginal bleeding for 2 years; she had had "kidney trouble" for 30 years. Since girlhood she had experienced recurrent attacks of fever, chills, pus in the urine, and pain in the back; the latter was worse on the right side. These attacks would occur about once a year. She had had frequent cystoscopic examinations, and at each she said her kidneys "were stretched." Except for diurnal frequency, she had no urinary complaints.

Urologic investigation was carried out at the clinic because of the long history of infection of the urinary tract. The excretory urogram originally was reported as probably normal except that the left kidney appeared slightly smaller than the right. Cystoscopy showed extensive scarring of the urethra with cicatricial urethritis and the presence of purulent material as the cystoscope was passed through the urethra. No unusual orifice was noted at that time. Subsequent cystoscopy with the patient under anesthesia revealed 2 openings in the urethra at the 5 o'clock position. The lateral orifice could not be catheterized. The more medial opening was catheterized and roentgenograms revealed the pocket of a urethral diverticulum.

Surgical transvaginal exploration was done 2 days later. The diverticulum that had been demonstrated by means of catheterization was found and excised. What was thought to be a second diverticulum was found and excised. This extended upward under the base of the bladder and was filled with purulent material. The patient's postoperative course was somewhat stormy and she continued to have chills, fever, and mild pain in the left loin. The fever subsided and she was dismissed from the hospital.

Low grade fever returned in a few days, with an increase in pain in the left loin. The patient was readmitted to the hospital and a cystoscopic examination was done. An opening from which purulent material exuded was noted in the floor of the urethra to the left of the midline. The opening was catheterized for a distance of approximately 6 centimeters. A roentgenogram was then made after injection of medium into this catheter. A left retrograde pyelogram also was made after passage of a No. 5 ureteral catheter into the left renal pelvis through the normally situated orifice in the bladder. These procedures demonstrated duplication of the left kidney and an ectopic opening of the ureter to the upper segment.

Surgical exploration was done in November, 1952, at which time a huge perinephritic abscess was found and drained. The kidney was not disturbed as it was considered that the risk to the patient was too great. The patient responded well to the drainage and returned in January, 1953, at which time a left nephrectomy was done.

COMMENT AND SUMMARY

I should like to re-emphasize the importance of the following points that have been mentioned in connection with diverticula of the female urethra. A carefully taken history often will give the necessary clues to the possibility of such lesions being present. When the severity of symptoms is considerable and the patient complains of great dysuria associated with a sense of fullness or pressure at the vaginal introitus with or without a mass, the presence of a diverticulum must be suspected. Such complaints associated with dyspareunia are most suggestive. Leakage of a small amount of urine shortly after voiding is another telltale sign.

Certain endoscopic instruments are not optically suited to proper examination of the female in the search for such lesions. The direct-vision cystoscope or urethroscope or the panendoscope are satisfactory for such examinations. Use of these instruments, coupled with roentgenologic study, will provide the means of diagnosis of these lesions.

A COMPARISON OF TALC AND ABSORBABLE STARCH POWDERS

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IN describing the first case of intraperitoneal granuloma due to talc, Antopol in 1933 inaugurated a study which has been extended by many investigators. Subsequent investigations followed two courses: the first pointing to the serious complications, sometimes fatal, that could ensue from the inadvertent implantation of talc at the time of operation; and the second, seeking a suitable innocuous substitute. The literature was extensively reviewed by Seelig and his associates in 1943. In the past decade many other investigators have been concerned with both the first course and the second. The substitute recommended by Seelig and his associates, potassium acid tartrate, has found other champions, but despite that fact it has not gained general acceptance because it hastens the deterioration of repeatedly autoclaved gloves. Today, starch chemically treated to prevent gelatinization upon autoclaving, without interfering with its ultimate absorption after implantation, is the most widely employed substitute for talc. The value of starch was initially reported by Lee and Lehman, and their results have been repeatedly confirmed.

At present, starch is treated either with epichlorohydrin or formaldehyde to confer upon it the desired properties. In addition, various additives are mixed with it to enhance its lubricity and flow properties.

The present study was undertaken firstly, to determine if the two different types of chemically treated starch would exhibit significant differences in their physiologic acceptability; secondly, to ascertain the influence of various additives in different concentrations upon the physiologic behavior of the starches; and finally, to investigate the variation with species of the rates of absorption of the starches after implantation and of the degrees of tissue reaction caused thereby.

From the Johnson & Johnson Research Foundation and the Research Division of Ethicon, Inc.

MATERIALS AND METHODS

The following materials were used in this study: 3 different samples of a formaldehyde starch, A, B, and C; 4 samples of an epichlorohydrin treated starch containing respectively 2, 10, 30 per cent magnesium oxide, and 2 per cent magnesium carbonate; 1 starch coated with aluminum stearate; and talc. Of the formaldehyde treated starches, all gave positive tests for free formaldehyde.

The materials were aseptically implanted intraperitoneally in guinea pigs and rabbits, and subcutaneously in rats. For the former, the methods of Walkling and Lindenmuth were employed; and for the latter, the procedures described by Frantz and Lattes were employed.

Guinea pigs weighing between 600 and 800 grams were operated upon under aseptic conditions. One hundred milligrams of the sterile powders were implanted into the peritoneal cavity of each animal. A sterile hemostat was used to spread the powder gently over the viscera. In control animals sham operations were performed in an identical manner, but no material was introduced into the animals.

Wistar rats, weighing 150 to 250 grams, were employed and the aseptic technique of Frantz and Lattes was used. Twenty-five milligram samples of each powder being tested were implanted in the loose subcutaneous tissue of the backs of rats. Sham operations were performed in a like manner, but no material was introduced into the animals.

The operative procedure for rabbits was similar to that used for the guinea pig, but in the rabbit 500 milligrams of the powder were implanted instead of 100.

Animals were sacrificed at varying intervals of time after implantation of the powder. The involved tissues were cultured. After gross study, sections were taken for histologic examination.

The following factors, as employed by Walkling and Lindenmuth, were considered in the evaluation of the intraperitoneal reactions: (1) the extent of absorption, (2) the degrees of edema or inflammation, (3) the presence or absence of infection, (4) extent and types of intra-abdominal adhesions, and (5) extent of granulomatous reaction and cellular response.

To permit the calculation of averages for both residue size and tissue reaction, numerical values were assigned as follows: small residue = 1; moderate residue = 3; large residue = 5; slight to moderate tissue reaction = 1; marked reaction = 3; extensive = 5.

As a further check on the gross observations, the tissues were studied microscopically under normal and polarized light.

The subcutaneous reactions in the rat were compared in respect to hyperemia, vascularity, and the amounts of residue remaining.

RESULTS AND COMMENTS

Comparison between epichlorohydrin treated starch, formaldehyde starches, starch with aluminum stearate, and talc in the guinea pig. The various starches were compared with talc in respect to their acceptability to tissues and to their rates of absorption when implanted into the peritoneal cavities of guinea pigs.

1. The extent of absorbability.—Inspection of the data reveals the following: (a) Talc showed the largest cumulative amounts of residue at autopsy; examination of the peritoneal cavities 10 days after implantation revealed that 5 of the 6 animals showed evidences of yellowish-white granulomatous nodules matted together on the surface of the bowel, peritoneum, and omentum. The appearance of this unabsorbable material after 10 days yielded a norm for adjudging the relative amounts of starch present after the same interval. (b) Epichlorohydrin treated starch and the 3 formaldehyde starches, A, B, and C, each evidenced minimal amounts of residue (small to very small). The absorption rates were different however; the formaldehyde starches A and B were absorbed completely within 5 days of implantation; whereas the epichlorohydrin treated starch and formaldehyde starch C required 10 days for complete absorption. (c) Of the starches, that with aluminum stearate showed the greatest residues, but they were less than for the talc. This starch too had been absorbed by the tenth day after implantation.

2. Edema or inflammation.—None of the powders tested evoked peritoneal inflammation of any significant degree.

3. Infection.—Smears taken of the peritoneal cavities of all animals were cultured in thioglycollate medium for 10 days. No bacterial growth could be detected.

4. Extent and types of intra-abdominal adhesions.—There were significantly fewer and less dense adhesions resulting from the implantation of the formaldehyde starch A. Epichlorohydrin treated starch and the formaldehyde starches B and C produced more adhesions than did the formaldehyde starch A, but still significantly less than did the other preparations used. The starch with aluminum stearate and talc evoked the greatest degree of abdominal adhesions (Fig. 1).

5. Extent of granulomatous reaction and cellular response.—Talc caused the greatest degree of cellular response. The formaldehyde starch A showed the least cellular reaction; epichlorohydrin treated starch, formaldehyde starches B and C, and the starch with aluminum stearate, all evoked a slightly greater cellular infiltration (slight to moderate degree) than the formaldehyde starch A (slight degree), but much less than did the talc (marked to extensive degree).

The microscopic examination of tissues in which talc was present showed reactions that were granulomatous, but with the macrophage predominating throughout a background of fibroblasts, monocytes, polymorphonuclear leucocytes, and multinucleated giant cells. Under ordinary light slightly bluish crystals of varying sizes and shapes were seen. Studies under polarized light revealed the crystals as doubly refractive and of irregular configuration.

Sections of the nodules and adhesions from the starch-implanted animals revealed them to be granulomas similar to those produced by talc, but with fewer fibroblasts and more mononuclear cells and polymorphonuclear leucocytes. Giant cells were also observed. When viewed by polarized light the starch granules manifested themselves as white spots of light having the characteristic dark Maltese cross configuration in their centers. This check on the absorption is essential to detect traces of unabsorbed starch which would be seen neither by the naked eye nor under a microscope with ordinary light.

Comparison between samples of epichlorohydrin treated starch containing varying amounts of magnesium oxide in rats. The per cent of magnesium oxide added to the epichlorohydrin treated starch did not significantly influence its absorption after subcutaneous implantation in rats. In general, tissue reactions were marked at 7 days, but had subsided by the fifteenth day postoperative, and repair was usually well advanced by the twenty-fifth day. There were only minor differences between the samples as to the degree of reaction.

Comparison in rats between samples of epichlorohydrin treated starch containing magnesium oxide or magnesium carbonate. This experiment was directed toward obtaining in rats similar comparative data on epichlorohydrin starch preparations in which magnesium carbonate had been added as a dispersal agent.

Absorption of the epichlorohydrin treated starch derivatives containing magnesium carbonate followed a more definite and reliable pattern than did those containing magnesium oxide. The absorption of the magnesium oxide preparations was somewhat irregular in that there was no clearly marked decrease in the amounts of residues remaining at each succeeding autopsy period. The formulation with magnesium carbonate, however, showed a definite increase in absorption in relation to the increasing intervals after implantation. In the case of all materials, however, absorption was complete at the end of 25 days.

The epichlorohydrin treated starch containing magnesium carbonate was noted to

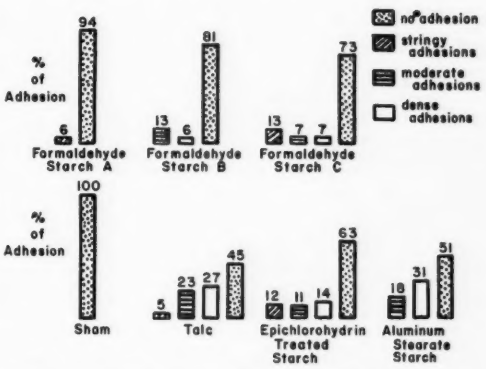

Fig. 1. Percentage and types of abdominal adhesions

have evoked only slight to moderate over-all tissue reactions, while those with the magnesium oxide produced a somewhat greater tissue irritation (moderate degree) through the fifteenth day postoperative.

Comparison in the rat between epichlorohydrin treated starch, formaldehyde starch, and starch with aluminum stearate. This study was devoted to comparing the tissue reactions evoked and the rates of absorption of epichlorohydrin starch, formaldehyde starches A, B, and C, and aluminum stearate starch when implanted subcutaneously in rats.

All of the starches tested in this experiment produced small masses grossly visible at autopsy; the epichlorohydrin treated starch evidenced the greatest amount of starch under polarized light; formaldehyde starch A showed the least. Formaldehyde starches A and C were completely absorbed within 15 days, whereas the epichlorohydrin starch, formaldehyde starch B, and the starch with aluminum stearate were completely absorbed within 25 days after implantation. All sites of implantation manifested minimal hyperemia and vascularity grossly. Likewise, all of the starch preparations tested evidenced the same cumulative over-all tissue reactions (slight to moderate degree).

Comparison in the rabbit between samples of epichlorohydrin treated starch containing magnesium oxide or magnesium carbonate. The study herein was devoted to comparing the physiologic responses in the peritoneal cavity

of the rabbit to epichlorohydrin treated starch in which magnesium carbonate had been added as a dispersal agent.

The fact that the residues of the epichlorohydrin treated starch with magnesium carbonate were large 25 days after implantation indicated that absorption of this sample was very slow and that a considerably longer period than 25 days would have been necessary for complete absorption. The epichlorohydrin treated starch had been completely absorbed by the twenty-fifth day after implantation. The nature of the inorganic salt used as an additive did not appear to influence significantly the adhesions produced.

Microscopically, sections of nodules and adhesions from the starch-implanted animals revealed granulomatous reactions comprised of fibroblasts, mononuclear phagocytes, polymorphonuclear leucocytes, eosinophiles, and multinucleated giant cells. Both the starch with magnesium oxide and that with magnesium carbonate evoked cellular infiltrations and over-all tissue reactions of a marked degree.

These experiments not only provided some insight as to the nature of the cellular reactions to the powders from the time of their introduction into animals until the time of their complete absorption, but also offered additional evidence as to the superiority of absorbable starch lubricants over talc in regard to their comparative innocuousness to tissues. This advantage of the absorbable starches is relative since the deposition in tissues of excessive amounts may cause undesirable responses.

All of the starch preparations tested showed widely differing responses in different species, an observation previously made by Postlethwait and associates. Graham and Jenkins also found that 5 species differed widely in responses when the peritoneal cavities were used. Neither this study nor any with which we are familiar has indicated which species the human would most closely resemble in reactions to starch.

SUMMARY AND CONCLUSIONS

1. Tests of talc and various absorbable starches containing different additives were made to determine the degrees of absorption, adhesions, cellular response, and over-all tissue reactions in the peritoneal cavities of the guinea pig and rabbit and in the subcutaneous tissues of the rat. The starches had been made autoclavable either by treatment with formaldehyde or by treatment with epichlorohydrin.

2. The addition of various percentages of magnesium oxide to epichlorohydrin treated starch had little effect upon its absorption rate.

3. In comparing the action of magnesium carbonate upon the absorption qualities of starch, it appeared that its effects were not strikingly different from those of magnesium oxide. However, it did favor a more regular absorption.

4. Although the modified starches are much more acceptable to tissue than talc, even these materials in excessive amounts can cause untoward reactions.

5. Further evidence has been adduced that talc is a deleterious substance in living tissue, that it produces a violent peritoneal reaction with adhesions, and that its use as a dusting powder for gloves is dangerous.

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A SURGEON'S CLASSIFICATION OF CARCINOMA OF THE STOMACH

Preliminary Report

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CLASSIFICATIONS of malignant disease should be simple and should yield useful information as to prognosis. Such a nomenclature can lead to clearer understanding of disease processes, to valid comparisons of treatment for similar stages of the disease, and ultimately to improved therapy.

From a surgical standpoint, current classifications of carcinoma of the stomach are not entirely satisfactory. One method, the Broders classification, depends solely upon the histologic picture and ignores, for example, extension of the disease beyond the stomach. It is obvious that a favorable prognosis based upon histology is nullified if the tumor is fixed to the aorta and is not resectable. The Borrmann classification (1, 2) is based solely upon the gross appearance of the tumor within the lumen of the stomach, and understandably has been utilized by gastroscopists. Again, however, it is evident that the favorable gross appearance of a tumor will not foretell a favorable outcome of the disease if metastases are already present in the liver. Many authors have stressed the significance of metastases to regional nodes, but no classification has combined the two factors that have the greatest bearing on prognosis: (1) the existence and location of metastases; (2) the degree of invasion by the primary tumor. A classification is proposed that is based upon these two factors: metastases and invasion.

Metastases. The extent of metastases is appraised preoperatively (for pulmonary or bone metastases, as an example) and at the time of surgery. Three stages are designated by capital letters (A, B, C) beginning with the most favorable stage, and ending with the least favorable stage:

Stage A—No metastases.

Stage B—Regional metastases to lymph nodes that are usually resectable.

Stage C—Distant metastases, connoting incurability.

Invasion. Invasion or local extension is determined by the surgeon at the time of laparotomy and is classified according to the degree to which the primary growth has penetrated the walls of the stomach. Three stages of invasion are recognized and are designated by Roman numerals (I, II, III), once more starting with the most favorable stage and ending with the least favorable stage:

Stage I—The growth is superficial and is confined to mucosa and muscularis.

Stage II—All gastric layers are involved, including the serosa, but there is no extragastric extension.

Stage III—The tumor has extended in continuity to neighboring structures, such as mesocolon, colon, liver, or pancreas.

In stages I and II the primary lesion always may be resected, whereas in stage III, the primary lesion may be resected only if the involved neighboring structures are resectable.

The state of the disease in any given patient at the time of operation may be expressed by a combination of the two symbols: *metastases* represented by a letter A, B, or C, and *invasion* designated by a numeral I, II, or III. Superficial cancer, for example, with no clinical or pathologic evidence of metastases, would be grouped as A-I, the most favorable type. At the other extreme, a cancer that has metastasized to the liver and also has invaded neighboring structures would be classified as C-III.[1]

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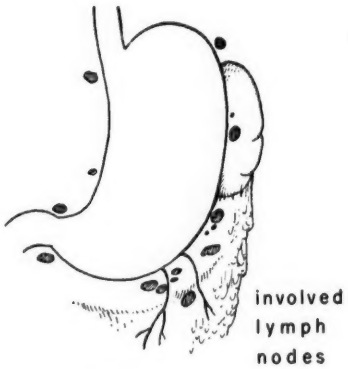
[1]For the special case of hopeless carcinoma where distant metastases are proved but there is no laparotomy, a group of C-NX is included, meaning that the stage of invasion of the primary tumor has not been determined. An example is the patient whose roentgenograms show a gastric neoplasm, but whose only operation is the biopsy of a supraclavicular lymph node containing metastatic carcinoma.

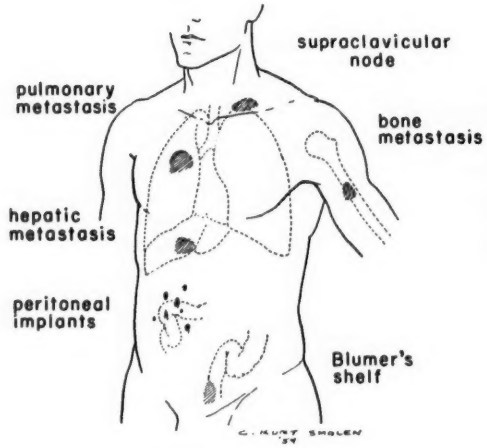
Stage A
No metastases

No metastases, grossly or microscopically.



Stage B
Regional metastases

Regional metastases, usually resectable. Must be verified histologically since involved nodes may appear normal grossly, and enlarged nodes may represent only chronic inflammation. These metastases will be resectable unless fixed to aorta or in gastrohepatic ligament.



Stage C
Distant metastases

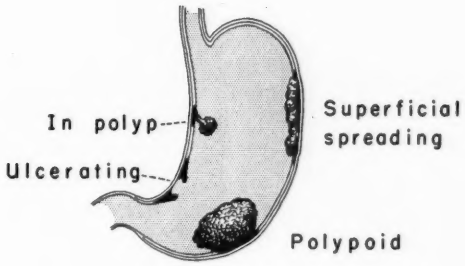
Distant metastases. Included are metastases to supraclavicular nodes, peritoneum, liver, lung, or bone. Usually will be verified histologically. At the present time they mean incurability.

Stage C-NX
Distant metastases
No operation

Distant metastases without surgical exploration of the stomach. A special case of stage C, such as might occur in a patient who has cancer in a biopsied supraclavicular lymph node, x-ray evidence of a gastric neoplasm, but no abdominal operation. "NX" is "No exploration" for grouping of invasion.

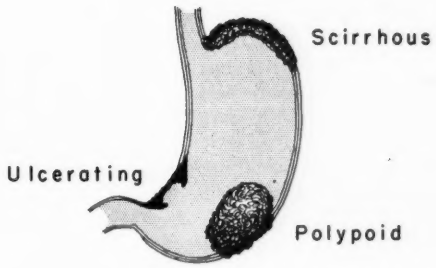
Fig. 1. a, Metastases.

Growth confined to mucosa and muscularis, irrespective of extent within the stomach. All are resectable.



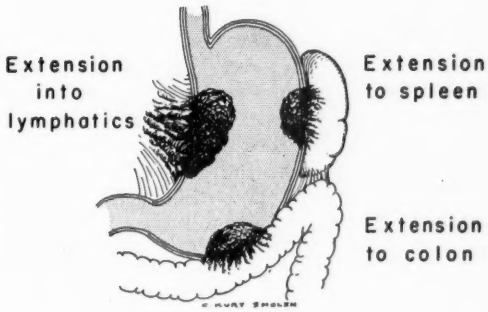
Stage I
Superficial cancer

Penetration to serosa but not involving extrinsic structures. Growths may extend into duodenum or esophagus if there is no external invasion. All are resectable.



Stage II
All gastric layers

Direct invasion of neighboring structures. These structures may be omentum, mesocolon, colon, pancreas, liver, spleen, diaphragm, aorta, adjacent lymphatics, or lymph nodes, or any combination of these. Resectability depends upon the structures that are invaded.



Stage III
Extragastric invasion

Fig. 1. b, Invasion.

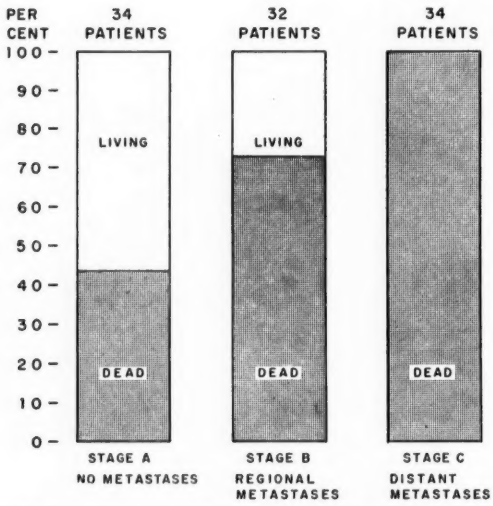


Fig. 2. Correlation between stage of metastases and prognosis, including all degrees of invasion by primary tumor, 100 patients with gastric carcinoma, 1 to 4 years follow-up.

A diagrammatic representation of the classification is given in Figure 1, with detailed definitions of the three stages of metastases and three stages of invasion.

PRELIMINARY STUDY OF PERSONAL SERIES BY THE NEW CLASSIFICATION

The proposed classification has been tested on a consecutive series of 100 patients each of whom had a primary operation for carcinoma of the stomach. The operations were performed in the years 1950, 1951, and 1952, and the follow-up is 100 per cent. The minimum period of 1 year is admittedly too short to determine curability, but it has proved long enough to demonstrate many of the failures. In Table I the breakdown of the data in the 100 cases is given, including the number of survivors through 1953.

In nearly every case it was simple to classify the tumor from information available in the operative notes and pathologic reports. In the 2 or 3 instances in which the grouping could not be clearly defined, it seemed probable that ambiguity would have been avoided if the classification had been borne in mind at the time the operative note was being dictated.

TABLE I.—CONSECUTIVE SERIES OF SURGICAL CASES OF GASTRIC CARCINOMA (FOLLOW-UP 1 TO 4 YEARS)

Stage	Total No. cases	Resection for cure	Living with disease	Living without disease
A-I	7	7	0	7
A-II	15	15	0	7
A-III	12	9	0	5
B-I	1	1	0	1
B-II	12	12	1	6
B-III	19	11	2	2
C-I	0	—	—	—
C-II	7	0	0	0
C-III	20	0	0	0
C-NX	7	0	0	0
Totals	100	55	3	28

The expected relationship between the stage of metastases and the prognosis is shown schematically in Figure 2. Nineteen of 34 patients in stage A with no metastases (A-I, A-II, A-III) are living without apparent disease (minimum of 1 year follow-up) whereas all 34 patients in stage C with distant metastases (C-I, C-II, C-III, and C-NX) are dead.

A definite relationship between the degree of invasion and prognosis is shown schematically in Figure 3. Stage C lesions with distant metastases have been omitted because of the hopeless outlook. Eight patients grouped as having A-I and B-I lesions are all living and apparently free from disease; 13 of 27 patients grouped as having A-II and B-II lesions are living and apparently free from disease; but only 7 patients among 31 grouped as having A-III and B-III lesions apparently are cured.

If these correlations hold with a longer period of follow-up, it will suggest that the classification has prognostic value.[1]

DISCUSSION

At the present time, survival rates for gastric cancer are often calculated with respect

[1]Studies by Ransom suggest that both correlations will hold qualitatively with a longer period of follow-up. In calculating 5 year survivors among 343 resections for "cure" in gastric carcinoma, he noted 16 per cent 5 year survivors if lymph nodes were involved, as opposed to 50 per cent if they were not involved. Similarly, there were 16 per cent 5 year survivors if there was perigastric involvement, but 35 per cent if there was no perigastric involvement.

to: (1) total number of patients having the disease; (2) total number of patients coming to operation; (3) total number of patients having a gastric resection. Survival rates determined from these totals are useful for measuring the over-all effectiveness of case detection and treatment within a particular hospital, but they are not adaptable for comparisons between different hospitals. For example, a charity hospital is likely to have a higher proportion of patients with advanced cancer than is a private hospital, and consequently will have a lower proportion of 3 and 5 year survivors. The proposed classification, based upon findings at the time of operation, will compensate for such obvious discrepancies and should permit comparison of results between different hospitals.

One potential use of the classification is in determining the place of total gastric resection in the treatment of gastric carcinoma. If it can be shown that the end results of total gastrectomy are superior to lesser procedures, group by group, even when the lesion is highly favorable (as in group A-I), it will be incumbent upon surgeons to employ total gastrectomy for all lesions.

A second potential use of the classification concerns the gastric ulcer problem. Classification of gastric ulcers explored solely because of the possibility of malignancy may conceivably disclose that many are types A-I and B-I, or highly favorable. This finding would combat the defeatist attitude of the physician who procrastinates in recommending surgery for gastric ulcer of uncertain etiology because he believes the prognosis is uniformly bad if the ulcer is malignant.

The classification makes no allowance for histologic types. The pathologist must, of course, distinguish the epithelial malignancies from the other kinds such as lymphosarcoma, Hodgkin's disease, or leiomyosarcoma. (The classification may prove to be appropriate for any type of malignant tumor, but most investigators will wish to consider carcinoma separately from the others.) This disregard of histology is not to be construed as a belief that the microscopic picture is of no consequence, but merely that it is of less prognostic significance than are metastases and invasion.

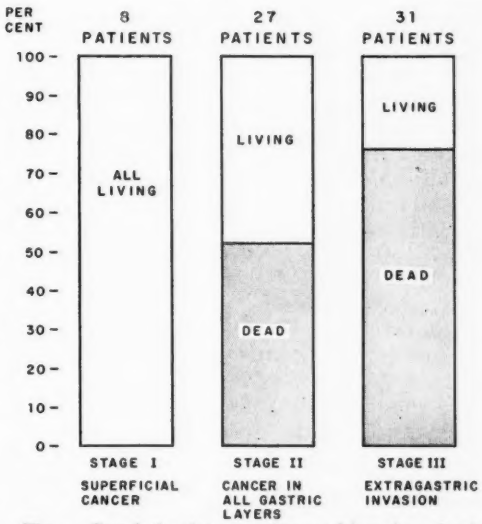


Fig. 3. Correlation between degree of invasion of primary tumor and prognosis, 66 patients with gastric carcinoma, 1 to 4 year follow-up (excluding 34 patients with distant metastases).

There can be no objection to further subclassification based upon histologic type, but inclusion of histology in the fundamental scheme of this classification would probably complicate it beyond its worth. Studies now in progress correlating the histology of gastric carcinoma with metastases and invasion already point up the poor prognosis associated with scirrhous type lesions.

SUMMARY AND CONCLUSION

1. Present classifications of carcinoma of the stomach are not entirely satisfactory to surgeons.

2. A simple classification based upon 3 stages of *metastases* and 3 stages of *invasion* by the primary tumor is presented: Metastases—stage A, no metastases; stage B, regional metastases; stage C, distant metastases. Invasion—stage I, superficial cancer; stage II, cancer in all gastric layers; stage III, cancer invading, by continuity, structures outside the stomach.

3. A combination of letter and numeral, the first representing the stage of metastases, the second the degree of invasion, designates the state of the disease in the patient at the time of operation. Thus, A-I represents a superfi-

cial cancer without metastases and implies a favorable prognosis.

4. The classification has been tested on a consecutive series of 100 patients, all of whom have been followed 1 to 4 years after operation. There is good correlation between the results to date and the prognosis implied by the classification.

5. It is hoped that this classification will help to clarify some of the current problems in the surgical treatment of carcinoma of the stomach.

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THE USE OF PLIABLE PLASTIC TUBES AS AORTIC SUBSTITUTES IN MAN

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ANEURYSMS of the aorta have long presented a particularly difficult problem in treatment since, until very recently, surgical methods of proved worth in the management of peripheral aneurysms did not seem applicable to these lesions. For one thing, saccular aneurysms of the aorta rarely have small mouths which are so often characteristic of peripheral aneurysms and which facilitate their extirpation with preservation of the continuity of the artery by lateral suture or excision and end-to-end anastomosis. For another, though peripheral lesions can often be treated by excision and ligation of the parent artery, the aorta cannot be suddenly and permanently interrupted without disastrous consequences. For still another, it was not known whether the aorta, and particularly its thoracic portion, could be safely occluded for sufficiently long intervals to permit excision and repair. Finally, though appropriate autogenous veins were available for bridging gaps in peripheral vessels, no autogenous vessel was suitable for interpolation in an aortic defect.

Efforts to treat aortic aneurysms by partial or complete ligation had yielded discouraging results. Attempts to control aortic aneurysms by wrapping them with reactive plastic membranes or injecting fibroplastic substances into their adventitial layers, and by introduction of coils of wire within then sometimes brought about remarkable palliation, but did not prove curative. In view of the distressing symptoms sometimes associated with aortic aneurysms and particularly in view of the poor prognosis attending them, there was great need for a method of definite treatment which would result in cure.

From the Department of Surgery, Indiana University Medical Center, Indianapolis, Indiana. Aided by a contract between the Office of Naval Research, the United States Navy, and Indiana University and grants from the James Whitcomb Riley Memorial Association and from the Indiana Heart Foundation.

Aneurysms associated with coarctation of the aorta constitute a special problem because of the excellence of collateral circulation about the obstructing lesion. That cases of this sort can be excised without restoration of aortic continuity and with temporary survival is demonstrated by the experience of Alexander and Byron (1, 2). An occasional case is also encountered which can be treated with complete success by excision, mobilization of the aorta, and end-to-end repair, as was true in a patient treated by one of us (20).

In recent years it has been demonstrated that saccular aneurysms arising from the aorta can often be managed successfully by clamping the mouth of the aneurysm and performing a lateral aortorrhaphy. This is evident from the experience of Ochsner, Meyer and his associates, Woods and Kenny, Cooley and DeBakey (6, 7), Bahnson (3), and Cowley and Yeager. The radical cure of certain saccular and all fusiform aneurysms of the aorta depends upon excision of the aneurysm and interpolation of a graft in the aortic defect.

Initial experiences with the use of aortic homografts were obtained in cases of aneurysms associated with coarctation of the aorta. Swan and his associates and Gross and his colleagues have reported successful experiences. It has subsequently become evident that these principles may be utilized in the cure of aneurysms not associated with coarctation. Lam and Aram used such a graft to bypass an aneurysm of the thoracic aorta. Though the graft remained open the patient subsequently expired because of sepsis in the isolated aneurysm which was left in situ. DeBakey and Cooley (9) obtained an excellent result by excising such a thoracic aneurysm and interpolating a graft. The same procedure has been shown to be applicable in cases of abdominal aortic aneurysms by a number of surgeons: Murray, Dubost and his colleagues,

Brock, DeBakey and Cooley (10), Bahnson (4), and Szilagyi and Hemmer. Successful cases have also been reported of use of arterial homografts in patients with aortic thrombosis. The results to date with the use of homografts in bridging gaps in the human aorta have been excellent. The grafts have remained patent, only 1 aneurysmal dilatation has been reported,[1] and in only a few instances has calcification thus far been noted.

In spite of the success which usually attends the use of homologous arterial grafts, it has been known since the early experiments carried out in the first part of this century that they do not survive as living structures but are replaced completely or in large part by new tissues from the host. Numerous carefully performed recent experiments with fresh arterial homografts and homografts preserved and stored by a variety of methods have confirmed these earlier observations. In general, preserved and nonviable or only questionably viable homografts appear to yield better results than fresh homologous vascular transplants. Since homologous grafts thus appear to function principally as physical struts which ultimately undergo host replacement, the question naturally arises whether their use offers any advantage over grafts made of some nonreactive inert foreign material. Should this prove to be the case, the difficulties connected with the acquisition and storage of homologous grafts would be eliminated.

Most efforts at permanent intubation of arteries with rigid inert tubes have proved unsuccessful. Use of paraffined silver tubes and tubes made of glass, aluminum, or gold plate have generally resulted in failure. Hufnagel and Gillespie (15) demonstrated, however, that finely polished tubes of methyl methacrylate could be inserted in the aortas of dogs with continued patency. By use of a technique of "multiple point fixation" one could avoid the hazard of ischemic necrosis of the aortic wall which so commonly occurs beneath the ligature used to fix any interpolated tube in place. Utilizing this principle, Hufnagel (14) has successfully inserted short valve-containing tubes of this material for the treatment of aortic insufficiency in man. In 1947 Gibbon treated a patient with a large aneurysm of the lower thoracic aorta by intrasaccular interpolation of a rigid plastic tube into the proximal and distal ends of the aorta, the tube being anchored in place by ligatures of heavy silk. The patient was relieved of his pain but died on the eleventh postoperative day of embolism to the superior mesenteric artery. Cowley and Yeager used a large polyethylene tube for replacement of a portion of the descending aorta following excision of an aneurysm. When the patient died 18 hours later from acute coronary insufficiency the tube was still in place and had not leaked or clotted.

If a tube of plastic material were to be used as an arterial graft it should ideally be pliable rather than rigid or semirigid and of such structure that it could be sutured in place rather than fixed to the aortic ends by ligature or the technique of multiple point fixation. No experience with the use of such pliable plastic tubes as vascular substitutes in man have thus far been recorded in the literature, though Vorhees, Jaretzki, and Blakemore had success with tubes of vinyon 'N' in replacing segments of aorta in dogs.

On July 25, 1953, we were confronted with the problem of treating a patient with a ruptured abdominal aortic aneurysm. No homologous aortic graft was available at the time. Experiences with the use of finely woven nylon in the repair of experimentally produced atrial and ventricular septal defects had demonstrated that this material was tolerated well within the heart, that its use was not associated with thrombosis, and that it became covered with an endothelial membrane. During these experiments one of us (H.K.) had interpolated into a few vascular defects tubes made of nylon which had been fused to a thin sheet of polythene. Subsequently an intensive study of this problem had been undertaken (21). Preliminary observations in the laboratory had demonstrated that tubes made of nylon could be nicely sutured in place in aortic defects by the same technique of arterial suture utilized for the interpolation of vascular grafts. Considerable loss of blood occurred

[1] In this exceptional case the aneurysm ruptured and brought about the death of the patient 6 months after implantation of the graft. (Brock, R. C. Aortic homografting; a report of 6 successful cases. Guy's Hosp. Rep., Lond., 1953, 102: 203.)

initially through the grafts, however, and it became evident that it would be advantageous to render the nylon tube impervious to blood. This objective was accomplished by placing a thin sheet of nonreactive polythene between 2 sheets of nylon and ironing the material with an iron adjusted to "wool." The low melting point of polythene as compared with the higher melting point of nylon was thus utilized to fuse together the 3 sheets of plastic material. Grafts of suitable diameter, length, and shape could then be fashioned by sewing sheets of this material into tubes with an ordinary sewing machine.

CASE REPORTS

CASE 1. The patient was a 70 year old white male who was admitted to the hospital on July 25, 1953, complaining of severe abdominal pain of a few days' duration. On March 14, 1953, he had been operated upon at another institution. At that time he was found to have a large arteriosclerotic aneurysm measuring 14 by 14 by 14 centimeters and beginning about 3.5 centimeters distal to the renal artery and extending to within 2.5 centimeters of the bifurcation of the aorta. A note from the institution stated that there was diffuse dilatation of the aorta both above and below the aneurysm. It was elected to reinforce the aneurysm with Ivalon sponge because of the fact that the patient was hypertensive and in poor general condition. This procedure was carried out and the patient had an uneventful postoperative convalescence.

A few days before admission he developed abdominal pain, and it became extremely severe on the day before admission. His physician had thought that the aneurysm had been expanding, and on the day before admission noted that the abdominal mass was getting larger rapidly. At the time of admission the patient looked acutely ill and was in excruciating pain. A very large mass was palpable in the abdomen extending to the right of the midline and bulging over into the left flank. The patient was in obvious circulatory collapse. Blood pressure was 100/60 and pulse 120. The erythrocyte count was 2.37 million and the hemoglobin 6.2 grams. The circulation to both lower extremities was adequate and both femoral and popliteal pulsations were palpable. It was obvious that his aneurysm had perforated and that the patient was in a near terminal state. He had not voided during the preceding 24 hours and catheterization yielded only 350 cubic centimeters of urine.

No homologous aortic grafts were available. Two grafts made of fused nylon and polythene were hastily constructed. Because the aorta above and below the aneurysm was said to have been markedly enlarged at the time of the first operation, the grafts were made larger than the size of the usual aorta.

Fig. 1. Photograph of specimen in Case 1. The aorta and graft have been opened and the inner surface of the proximal portion of the graft and its point of union with the aorta are shown. The graft is seen to have a smooth lining.

Two hours after admission the patient was taken to the operating room. A long midline incision was made. Abdominal exploration revealed that the patient's aneurysm had perforated and that bleeding had occurred throughout all of the retroperitoneal tissues on the left side and into the abdominal wall. The aneurysm was found to be considerably larger than that described at the time of his first operation. It began about 1.5 centimeters below the level of the renal arteries and extended into and included both common iliac arteries. No pulsation could be felt in the left external iliac artery. When the proximal aorta was isolated it proved to be normal in size. There was, therefore, a great discrepancy in size between the prepared grafts and the patient's aorta. It was then observed that the iliac extensions on one of the grafts approximated the size of the aorta proximally and the right iliac artery distally and that one of these limbs could be used to connect the aorta to the right iliac.

It was realized that the use of this graft would necessitate ligation of the left common iliac artery. However, in view of the patient's desperate situation it was believed that this course of action would result in his best chance of survival even though one extremity might be lost. Therefore, the vessels entering the aneurysm were occluded, the sac was opened, and a great portion of it was excised. The plastic graft was anastomosed to the aorta and the right common iliac artery. The left common iliac was ligated. When the clamps were released very little leakage of blood occurred from the sites of anastomosis.

From the time of the operation there was an excellent pulse in the right femoral and popliteal artery

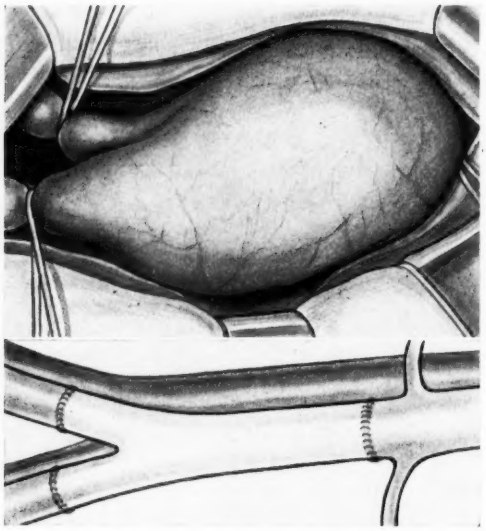

Fig. 2. a, Sketch of the aneurysm in Case 2 and, b, of the graft inserted from photographs made at time of operation.

and the right lower extremity maintained excellent color and warmth. The left lower extremity, however, was totally ischemic up to the midthigh. The oliguria present on admission continued. During the next 10 days the average urinary excretion was about 200 cubic centimeters per day. During this time the serum electrolytes were maintained at a near normal level. The serum potassium was kept within safe levels by the use of exchange resins and gastric suction. The patient eventually died in uremia. Throughout his postoperative course the pulsations in the right leg remained excellent and it was obvious that the plastic aortic graft was functioning well.

Postmortem examination revealed the graft to have a thin, smooth, glistening lining (Fig. 1). On microscopic examination it was seen to be composed chiefly of fibrin. Examination of the kidneys revealed evidence of lower nephron nephrosis.

Following the treatment of the first patient the study of plastic grafts for aortic replacement was intensified in the experimental laboratory. The results obtained were so satisfactory that it was thought that further clinical trial was warranted.

CASE 2. The patient was a 59 year old white male who was admitted to the hospital on October 25, 1953. About 11 months before admission the patient first noticed strong pulsations in his abdomen. In May 1953 his physician discovered an abdominal aneurysm. He was observed for a few months and then referred to the hospital for evaluation. Physical examination revealed a blood pressure of 140/95 and a pulse of 80. A large, firm, pulsating mass was found in the abdomen. It extended from 10 centimeters above the umbilicus to 9 centimeters below it and was palpable farther to the right than the left of the midline. It was believed that the aneurysm involved the right and possibly the left common iliac arteries.

Serologic tests for syphilis were negative and results of hematologic studies and urinalysis were within normal limits. The chest roentgenogram showed the heart to be normal in size and the aorta to be tortuous. The electrocardiogram was normal. On October 29 exploration was carried out through a long midline incision. The aortic aneurysm extended from the level of the renal vein down to and including the bifurcation of the aorta (Fig. 2a). The aneurysm was dissected free except where it was intimately adherent to the vena cava. The proximal aorta and the two common iliac arteries were isolated and then clamped. The aneurysm was opened and the major portion of it was excised. Only a thin strip of the wall of the aneurysm which was adherent to the vena cava remained. A plastic nylon-polythene graft of proper size was selected and sutured to the aorta above and to the two iliac arteries below (Fig. 2b). When the clamps were released only a small amount of blood was lost at the suture line. Pulsations were good in both iliac arteries. By the time the abdominal wound was closed good color and warmth had returned to both lower extremities. Pulses were excellent in the right femoral, popliteal, and posterior tibial arteries and in the left femoral artery.

An hour after completion of the operation pulsations were still not palpable below the proximal portion of the left common femoral artery and oscillometer readings were zero in the left midthigh. Although it was obvious that the circulation to the left extremity was adequate at rest, it was thought that the left femoral artery should be explored. The patient was, therefore, returned to the operating room where under local anesthesia the left femoral artery was exposed. An embolus was found at the femoral bifurcation which consisted of a portion of the partially calcified and organized thrombus which had lain within the aneurysm. Good retrograde blood flow occurred from the femoral and profunda femoral arteries. However, pulsations in the dorsal pedal and posterior tibial arteries were not present at the completion of the procedure.

The patient's postoperative course was excellent. Although circulation to the left lower extremity continued to be adequate, as evidenced by normal color and warmth, it was decided that another attempt should be made to relieve the obstruction of the femoral artery. On November 7 the left femoral artery was re-explored. The proximal portion of the common femoral, the superficial femoral, and the profunda femoral arteries were found to be patent but the major portion of the common femoral was obstructed. The thrombus was removed and heparin was administered. A small plastic tube was passed

easily down the superficial femoral artery to the region of the midportion of the popliteal artery and no obstruction was encountered. At the completion of the operation, although the superficial femoral artery seemed to be pulsating nicely, no popliteal dorsal pedal or posterior tibial pulsations could be felt. Anticoagulant therapy was continued for the next 6 days. At the time of discharge pulsation was present down to the region of the femoral bifurcation but not below this level.

Following discharge from the hospital the patient has been seen at intervals. No mass has been palpated in the abdomen and the abdominal aortic pulse is normal. The arterial pulsations and oscillometer readings in the right lower extremity have remained excellent. The left common femoral pulse is normal but no pulsations can be felt below this level. The color and temperature of the left lower extremity remain normal. The patient's only complaint has been a feeling of fatigue in the left leg after walking a distance of from 2 to 4 blocks. He has returned to work to normal activity.

CASE 3. The third patient was a 69 year old white male who was admitted to the hospital on November 30, 1953, with the chief complaint of epigastric pain. About 3 months before admission he noticed the onset of an intermittent throbbing pain in the epigastrium and became conscious of pulsations in his abdomen. One month before admission he was examined by his physician who found a large, pulsating, abdominal mass. Following this examination progressive enlargement of the abdominal tumor was noticed by both the patient and his physician.

Past history revealed 2 episodes of myocardial infarction, the first in 1942 and the second in 1947. These attacks were preceded and followed by the anginal syndrome, and at the time of admission the patient was carefully limiting his activity and taking nitroglycerine. In April 1952 the patient had a cerebrovascular accident with temporary loss of control of his extremities, followed by complete functional recovery.

Physical examination revealed a blood pressure of 120/110 and a pulse of 76. The left border of the heart was at the midclavicular line. The cardiac sounds were faint. No thrills or murmurs were present and the rhythm was regular except for occasional extrasystoles. Abdominal examination revealed a large, firm, slightly tender, pulsating mass which could be palpated from the xiphoid to the lower midabdomen. The mass could also be felt to extend to just above the prostate by digital examination of the rectum.

Serologic tests for syphilis were negative and complete blood count and urinalysis were within normal limits. The chest roentgenograms showed marked dilatation and tortuosity of the aorta, and slight left ventricular enlargement. The electrocardiogram revealed definite evidence of an old posterolateral myocardial infarction and multiple premature ventricular extrasystoles were present. A diagnosis of generalized arteriosclerosis, arteriosclerotic heart disease with angina pectoris, and abdominal aortic aneurysm due to arteriosclerosis was made.

Fig. 3. Photograph of graft, adjacent aorta, and external iliac arteries in Case 3.

On December 2 operation was carried out through a long midline incision. A huge thin-walled aneurysm of the aorta was found. At its upper end the aneurysm extended to the level of the liver and underneath the costal margin, and inferiorly it extended almost to the bottom of the pelvis. It was found to originate only a few millimeters below the renal arteries and involved both common iliac arteries. Shortly after the operation was begun and before dissection of the aneurysm was started, and before any loss of blood occurred, the patient's blood pressure began to fall precipitously and was difficult to maintain with neosynephrine. Electrocardiographic tracings showed that the patient had developed a first degree bundle branch block. The possibility that the patient had suffered another myocardial infarction was considered but no definite evidence was demonstrated by the electrocardiograms. In spite of these difficulties and the obvious risk, it was decided to continue the operation because it was thought that the aneurysm was so near the point of rupture that the patient would almost certainly be condemned to a fatal outcome in the very near future if nothing were done. Accordingly, the sac was dissected free except where it was intimately adherent to the lower portion of the vena cava and the right common iliac vein. In dissecting around the left common iliac artery considerable venous bleeding occurred. This was controlled by applying a gauze pack to the area. Blood loss was replaced in adequate amount. The aorta was clamped proximal to the origin of the aneurysm and the two external

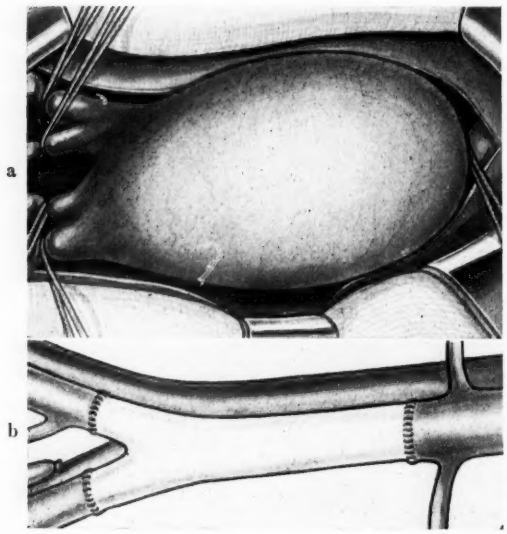

Fig. 4. a, Drawing of aneurysm in Case 4 and, b, of the interpolated graft.

iliac arteries were occluded distally. The aneurysm was opened widely and was largely excised. A nylon-polythene plastic graft was then sutured to the aorta above and to the external iliac arteries below. Good pulses were felt immediately in both femoral arteries. The remaining portion of the aneurysm in the pelvis was unroofed, but the base of it could not be safely removed. There was a slow ooze of blood from this area. It was controlled by interrupted sutures and pressure. At the time of closure it seemed that adequate hemostasis had been achieved.

The patient was sufficiently awake to speak a few words about half an hour after completion of the operation and seemed to be in good condition. Shortly thereafter, however, the blood pressure fell precipitously and he lost consciousness. The pulse did not increase in rate but remained slow and regular. The hypotension did not respond to administration of blood, plasma, or norepinephrine. Respirations became so shallow that trachial intubation was carried out so as to permit assisting of respirations. Oxygen was given. None of these measures were, however, effective, and the patient expired about 4 hours after being returned to his bed.

The terminal course of events was difficult to understand. It was thought that the blood loss at the time of operation had been replaced. An additional 2 liters of blood were given afterward since it was thought likely that some intra-abdominal bleeding may have taken place. The failure of blood and norepinephrine to correct the hypotension or alter his downhill course and the bradycardia in the presence of a low blood pressure cast doubt upon blood loss as the cause and raised the question of primary cardiac origin, or possibly of a cerebrovascular accident. Postmortem examination did not provide a satisfactory explanation. There was a large, old, myocardial infarct, but no fresh one. There was a large retroperitoneal hematoma and about 500 cubic centimeters of bloody fluid in the peritoneal cavity. The total amount of blood was less than that given during the postoperative period. The blood loss seemed to have occurred from the raw surface of the remaining portion of the wall of the aneurysm and the plastic graft and the anastomosis were in good condition (Fig. 3).

CASE 4. The patient was a 70 year old white male who had been first admitted to the hospital in January 1954 because of abdominal pain of 1 year's duration. The pain was rather severe and constant. During the preceding few months it had become more severe and narcotics had been required rather regularly. Sometimes the pain extended into the right lower extremity. In December 1953 he had been explored for gallbladder disease. A large aortic aneurysm had been discovered. His health had otherwise been good except for troublesome hemorrhoids. He had had large varices in both lower extremities for years. At the time of his first admission physical examination was not remarkable except for a large aneurysm of the abdominal aorta, varicosities of both lower extremities, and hemorrhoids. Serologic tests for syphilis were negative. Results of urine and hematologic examinations were normal. Findings at roentgenographic examination of the chest were essentially negative. Electrocardiographic study, much to our surprise, revealed clear evidence of a recent anterolateral myocardial infarction. There were multiple premature ventricular and auricular systoles. He was discharged from the hospital to his home and was readmitted 2 months later on March 15.

The aneurysm was little if any larger than it had been before. Pulses were excellent in both lower extremities. Electrocardiographic tracings showed evidence of an old anterior infarction. There were multiple premature ventricular systoles. Operation was carried out on March 18 through a long midline incision. The aneurysm was quite large and extended up to within less than a centimeter of the renal artery (Fig. 4a). It involved the aortic bifurcation and both common iliac arteries. It was excised except for a thin strip of aneurysmal wall left attached to the vena cava and a nylon-polythene graft was sutured to the aorta above and to the right common iliac and the left external iliac arteries below. Both common iliac arteries were partly calcified and markedly sclerotic. On the left, such a short stump of common iliac remained after excision of the aneurysm that it was believed necessary to ligate the hypogastric and anastomose the graft to the external iliac. A bilateral lumbar sympathectomy was performed. The patient stood the procedure well.

His convalescence was uneventful. Circulation in both lower extremities is excellent and bounding femoral, popliteal, and posterior tibial pulses are present.

By the time the next patient was treated sufficient animal experience with the use of methyl methacrylate coated nylon tubes had been accumulated so as to justify its trial in man.

CASE 5. The patient was a 77 year old white male who had had vague epigastric discomfort for 6 months and in whom a diagnosis of aneurysm of the abdominal aorta had been made in January 1954. He was admitted to the hospital on March 31. There was a large abdominal aortic aneurysm. Blood pressure was 150/90. Serologic tests for syphilis were negative, upon examination urine was normal except for a faint trace of albumen and results of hematologic studies were within normal limits. Radiologically the thoracic aorta was seen to be tortuous and dilated. Electrocardiograms showed multiple premature ventricular systoles as well as a 1 degree auriculoventricular block with PR interval of 0.22.

He was operated upon on April 2. The aneurysm originated about 1.5 centimeters below the renal arteries and extended downward to involve both common iliac arteries (Fig. 5a). It was excised and a graft of nylon coated with methyl methacrylate was sutured to the aorta above and both common iliac arteries below. In several places the graft had been punctured with the needle and withdrawn for more precise placement. Considerable bleeding occurred for a short while from these points.

The patient had a satisfactory convalescence. He was discharged from the hospital on April 17. He has excellent femoral, popliteal, posterior tibial, and dorsal pedal pulses, and both feet have maintained excellent circulation.

CASE 6. The patient, a 75 year old white male, was admitted on April 6, 1954. He had a large abdominal aortic aneurysm. Blood pressure was 150/80. Serologic tests for syphilis, electrocardiograms, urinalysis, and hematologic studies were normal. Chest radiograms revealed calcification of the aortic arch. Nonprotein nitrogen was 53 milligrams per cent. He was operated upon on April 9. There was a large aneurysm which arose about 6 centimeters below the renal arteries and involved both common iliac arteries. A second smaller aneurysm lay proximal to the larger one. It was about 4 centimeters in diameter. A third, about 2 centimeters in diameter, was situated in the right common iliac just below the larger aneurysm. All 3 were excised (Fig. 5b) and a nylon-polythene graft was sutured in place.

His convalescence was satisfactory and his feet have maintained excellent circulation, all pulses in the lower extremities being full. He was discharged from the hospital on April 21.

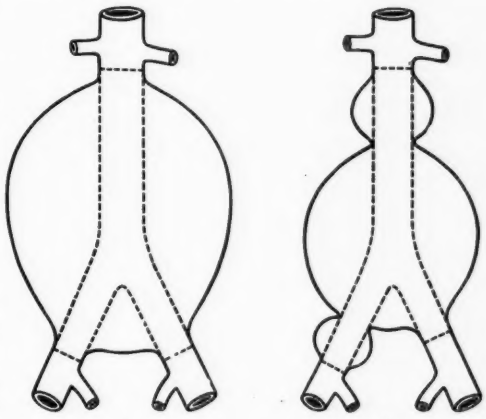

Fig. 5. Schematic drawings of aneurysms in, a, Case 5 and, b, Case 6 and of the grafts inserted.

DISCUSSION

It is obvious that certain advantages will accrue if aortic and aortic-bifurcation grafts of plastic material will serve as satisfactorily as our few clinical experiences and our more extensive experimental studies indicate they do. They are constructed of inexpensive and readily obtainable, thin, finely woven nylon cloth. They are easily and quickly prepared. They can be made of any size and shape. Thus a number of them can be made available so the surgeon can select a suitable one at the time of the operation. Though thin and pliable they have great tensile strength. They can be sterilized by autoclaving. They can be sutured to the ends of the vessel by ordinary techniques of vascular anastomosis. Experimental observations demonstrate that a strong new fibrous aorta with a smooth inner lining is developed about the inert graft from host tissues.

In the original important contribution of Voorhees, Jaretzki, and Blakemore with tubes of vinyon 'N' the material was not rendered impervious to blood. It was stated that bleeding occurred at first through the wall of the tube but eventually ceased. Our preliminary studies with tubes of untreated nylon demonstrated that such bleeding was an annoying and sometimes disastrous occurrence. It seemed evident that it would be desirable to obviate such bleeding. Treating nylon cloth

with plasma and thrombin did not achieve this objective. It was attained by fusing a thin sheet of nonreactive polythene between 2 sheets of nylon, and 5 of the 6 grafts used in the cases reported were of this material. Subsequent laboratory studies showed that the same objective could be achieved by coating the nylon with methyl methacrylate, and a graft of this sort was used in 1 patient.[1]

In all 6 cases the graft functioned well. The first patient was operated upon in a state of shock and died ultimately of lower nephron nephrosis. The graft was patent and lined with a smooth layer of fibrin. The second patient has a properly functioning graft 6 months after operation. In the third case the graft was working well at the time of death some hours after completion of the operation. A good aortic pathway has been re-established in the fourth, fifth, and sixth cases. In all of them the graft was sutured in place without difficulty.[2]

It is apparent that much additional work must be carried out in order to learn more about the usefulness and limitations of these grafts. Such investigations are in progress in the laboratory. In the meantime we believe that the results in these cases combined with the experimental studies justify the expansion of our clinical observations concerning the use of pliable plastic tubes for replacement of the aorta and aortic bifurcation.

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[1]Long term observations lead us to believe, however, that these grafts are inferior to those made of nylon and polythene.

[2]Since this paper was submitted for publication 4 additional cases of aneurysms of the aorta and aortic bifurcation have been treated successfully with use of nylon-polythene grafts.

HERNIAS OF SUPRAVESICAL FOSSA PRESENTING EXTERNALLY THROUGH THE CONJOINED TENDON

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SURGICAL periodicals and standard texts contain numerous articles on hernias but few references are made to the supravesical variety of direct inguinal hernia. In current monographs devoted solely to hernias, little attention is given to the type which is the subject of this paper.

Contrary to the impression that one would gather from the relative dearth of descriptive material on the subject, we have been increasingly impressed in recent years by the frequency of this hernia and have found that its clinical manifestations and prognosis following repair are quite different from the ordinary direct inguinal hernia.

We believe that in most statistical analyses this hernia has probably been included under the heading of direct inguinal hernia and that, therefore, its significance as a separate entity has been lost. There is further evidence that small, unrecognized supravesical hernias are not uncommonly present at the time of repair of indirect inguinal hernias and may constitute a source of recurrence.

Definition. A supravesical hernia is one in which the sac develops from the anterior parietal peritoneum of the supravesical fossa and manifests itself externally through an opening in the conjoined tendon. This hernia has also been called medial direct (as opposed to the more common lateral direct) because it is located medial to Hesselbach's triangle where the posterior inguinal canal wall consists only of transversalis fascia (Figs. 1, 2).

Sources of this study. This investigation is based upon 42 hernias seen between 1946 and 1954 in 41 patients. (One patient had a bilateral supravesical hernia.) Of the 41 patients, 16 had had previous herniorrhaphies.

Surgical anatomy. The essential defect in the anterior abdominal wall occurs in the conjoined tendon rather than in the transversalis fascia of Hesselbach's triangle which is the site of weakness in the ordinary direct inguinal hernia (Figs. 1 and 3).

The hernial ring is always found in the portion of the inguinal falx which is just superior and slightly lateral to the pubic tubercle (Fig. 3). The ring is mostly oval in shape; occasionally it is circular. It may vary in size from 0.7 to 3.5 centimeters in greatest dimension. The commonest size is about 1.5 by 0.5 centimeter. The edges of the ring are sharp and distinct and possess good tensile strength. The greater diameter of the oval defect is always parallel with the fibers of the conjoined tendon. The latter is usually tendinous or musculotendinous at this level. The lateral edge of the ring is usually about 1.5 centimeters medial to the lateral edge of the tendon, but varies with the size of the ring.

The connection of the hernial sac with the peritoneal cavity is in the supravesical fossa of the anterior abdominal wall. This fossa is bounded medially by the median umbilical fold created by obliteration of the urachus and laterally by the lateral umbilical fold formed by the obliterated umbilical artery. The latter runs from its origin at the site of the anterior division of the internal iliac artery in a direction which is superomedial, ending at the umbilicus. At the level under discussion, it is behind and parallel with the lateral border of the conjoined tendon. The herniation in the anterior parietal peritoneum occurs just medial to this fold (Fig. 3). Were the defect to be present lateral to the fold, the hernia would not protrude through the conjoined tendon but through that part of the posterior inguinal canal wall in which only the transversalis fascia lies anterior to the peritoneum and its fatty envelope.

The hernial sac varies in size. It is commonly several centimeters wider in its mid-

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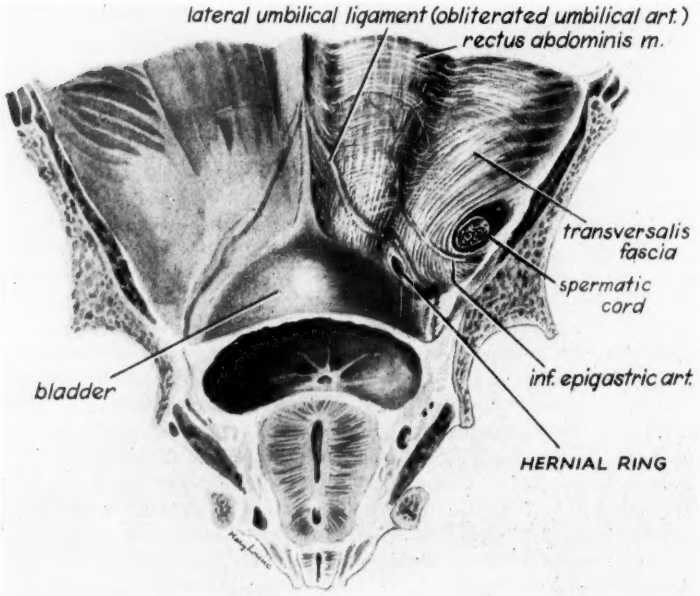

Fig. 1. View of internal surface of anterior abdominal wall. The parietal peritoneum and extraperitoneal fat have been removed. Note the location of the hernial ring medial to the lateral umbilical ligament in the part of the conjoint tendon lateral to the lateral border of the rectus abdominis muscle.

portion than at its neck and may vary from 3 or 4 centimeters to 10 centimeters in length. The sac lies posteromedial to the spermatic cord (or round ligament in the female) and extends through the external inguinal ring toward the scrotum (or labium majus) (Fig. 2). As it passes through the abdominal wall, it picks up its coverings. Thus, immediately surrounding the sac there is almost always an abundant fatty layer derived from the extraperitoneal fat. This fatty layer appears to be of a more solid consistency than the extraperitoneal fat. Although most of our patients were in the older age groups and tended to be obese, even in lean individuals the fatty envelope surrounding the sac appeared to be greater than one would expect from the distribution of fat elsewhere in the abdomen. Surrounding this layer of fat, there is connective tissue derived from the areolar coverings of the conjoined tendon.

It is this entire mass, consisting of hernial sac, surrounded by fat and encased in connective tissue, which protrudes through the external ring and, coursing parallel with the spermatic cord, extends toward the scrotum.

In most cases the urinary bladder is found adherent to the inferior surface of the sac, particularly in larger hernias. If the hernia is small, the bladder may be pulled through the ring in the conjoined tendon as tension is made on the sac during dissection.

CLINICAL FEATURES

Symptoms. Symptomatically, the patients differ little from those with the more usual types of hernias. Only 5 patients could recall an inciting cause, such as lifting a weight, and pushing a refrigerator. Of these 5, four were compensation cases. The others could remember no event which precipitated the hernia.

The duration of the hernias varied from 1 month to 24 years, as listed in the following: 1 month to 1 year in 17 cases; 1 to 5 years in 8 cases; 5 to 10 years in 9 cases; and 10 to 24 years in 5 cases; unknown in the others.

TABLE I.—DISTRIBUTION OF CASES

	Current series of supravesical hernias No.	Total No. inguinal hernias, of all types, repaired, current authors	Vogeler's collected series* of supravesical hernias
Sex distribution			
Male	34	207	35
Female	7	27	5
Side			
Left	25		16
Right	17		28
Age distribution, years old			
20–30	1		1
31–40	3		9
41–50	7		7
51–60	20		11
61–70	10		6
71–80			2

*Vogeler, K. Die supravesicalen Hernien. Beitr. klin. Chir., 1920, 118: 318.

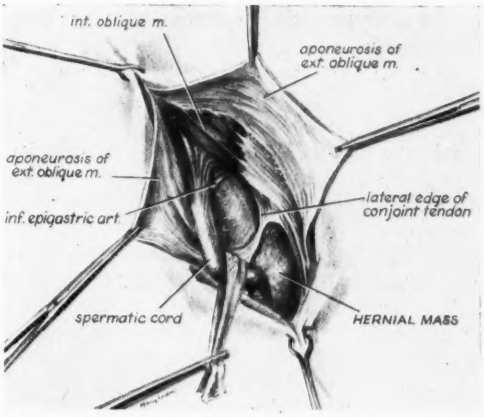

Fig. 2. View of right inguinal canal. The spermatic cord has been retracted laterally to expose the hernial mass which lies behind it and which protrudes through a defect in the conjoint tendon.

The complaints consisted, for the most part, either of no symptoms but knowledge of a mass in the groin, or mild aching pain in the inguinal area aggravated by standing or exercise. In only 3 cases did generalized abdominal cramps or diffuse noncrampy pain occur. In 2 of these cases, 1 male and 1 female, operation revealed strangulated small intestine; in the other, also a female, a strangulated epiploic appendix was found.

On physical examination, the external inguinal ring is usually narrow, resembling more the type of ring found in indirect hernias, although occasionally it may be dilated. There is an elongated or globular mass, depending on the size of the hernia and surrounding fat, extending through the ring toward the scrotum. The mass is soft and typically is either incompletely reducible or reduces into the inguinal canal with difficulty. Because of these facts, the hernias were often diagnosed clinically as being indirect. The transmitted impulse on coughing often is not as pronounced as with the usual hernia of similar size.

If the external ring is wide enough to admit the examining finger and the hernial mass can be sufficiently reduced or displaced, a small oval defect may be felt in the conjoined tendon superior to the pubic tubercle. The palpation of this defect fully establishes the diagnosis. When this defect was not palpated, the hernia was usually diagnosed as being indirect.

The distribution as to sex, side, and age is shown in Table I. Thus, 90 per cent of the patients in the current series of supravesical hernias were over 40 years of age and 73 per cent over 50. In the overall series of herniorrhaphies performed for all types of inguinal hernia, 87 per cent of the patients were over 40 years old and 68 per cent over 50.

Incidence. Between August 1949 and August 1953, 13 per cent of all inguinal herniorrhaphies performed were for the supravesical variety. This rather high percentage refers only to operative cases. During this same period, a considerable number of patients in the older age groups who had asymptomatic direct inguinal hernias were examined but were not operated upon. If these nonoperative patients were included in this series, the proportion of supravesical hernias would be considerably lower.

Contents of hernial sac. In 34 patients the sacs were empty at the time of operation. In 2 patients, strangulated small intestine was found. In another, an epiploic appendix had strangulated and required resection. One patient had omentum within the sac which was not adherent; in 3 others the omentum was held within the sac by adhesions which had to be severed. One patient who had had 3

previous herniorrhaphies had a diverticular outpouching of the cecum through the sac.

SURGICAL TREATMENT

Forty of the 42 hernias were repaired by operative treatment as follows:

The inguinal canal was opened in the usual manner and the spermatic cord separated from the hernial mass (Fig. 2). The connective tissue covering the latter was circumcised at the level of the anterior surface of the conjoined tendon and the covering was either removed or opened. The extraperitoneal fat was then incised along the superior surface of the hernia, near its apex, and the sac opened. (The superior surface is selected for opening of the sac rather than the inferior so that the possibility of opening the urinary bladder may be avoided.) The extraperitoneal fat was cleared off the sac to a level that was posterior to the hernial ring. In order to achieve this, the urinary bladder was frequently dissected away from the inferior surface of the sac. The neck of the sac was doubly suture ligated with chromic catgut and the excess of sac excised, following which the redundant extraperitoneal fat was removed (Fig. 3). If a portion of the urinary bladder protruded through the ring, it was replaced. The ring in the conjoined tendon was then approximated with No. 34 stainless steel wire sutures, the sutures being passed perpendicular to the direction of the fibers of the tendon. The spermatic cord was then explored for evidence of a small indirect hernia, hitherto unsuspected. The aponeurosis of the external oblique muscle was approximated in an overlapping manner posterior to the spermatic cord with the use of No. 32 and No. 34 wire sutures, and thus the cord was transplanted into the subcutaneous space. The skin was closed with silk sutures.

In 2 patients, the portion of the conjoined tendon lateral to the hernial ring was considerably thinned out because of the size of the ring. Consequently, the medial edge of the ring was sutured to Cooper's ligament, the remainder of the repair being the same.

In 1 patient silk was used rather than wire and catgut.

Follow-up of cases and results. The patients have been studied over a period of 1 to 78 months following operation. Twenty-two were followed for less than 6 months; 4 were observed for 6 months to a year; 9 more for 1 to 2 years; and 6 patients were seen for more than 2 years.

There have been no recurrences of a supravesical hernia. There were 16 patients who had had previous herniorrhaphies for the more usual types of hernias; of these, 2 patients had had 2 previous repairs and 1 had 3 previous hernioplasties. Nevertheless, even in this group, where ordinarily the rate of recurrence is higher, no evidence of reappearance of a supravesical hernia could be found. In this latter group of 16, the duration of follow-up was less than 6 months in 10, between 6 and 12 months in 2, and over a year in 4.

Two patients developed evidence of indirect hernia within 4 months following operation for supravesical hernia. Inasmuch as the spermatic cords were transplanted under the skin, the new external rings were located opposite the internal ring, and a small unsuspected indirect hernia could make its appearance within a short time after surgery. It is believed that both of these patients had small indirect hernias which were undetected at the time of operation, and the major hernia found—the supravesical one—alone was repaired.

DISCUSSION

It is evident that supravesical hernias occur mainly in older age groups and are more common than is generally realized. It is probable that in this series the incidence is high because these patients are drawn from clinical material with considerable geriatric emphasis.

The diagnosis can be made preoperatively on the basis of distinct physical findings. Before we became fully aware of the nature of this hernia, it was most frequently mistaken for an indirect inguinal hernia.

Although this hernia is classified as being of the direct variety because it is medial to the inferior epigastric vessels, it bears little anatomic, clinical, or prognostic resemblance to the more common direct hernia occurring in Hesselbach's triangle. Generally this hernia is smaller than the usual direct one and is accompanied by a narrow external ring. On physical examination, this hernia usually re-

duces either with difficulty or incompletely and gives a poor impulse on coughing. If the hernia can be completely reduced, the defect in the conjoined tendon may be palpated. The posterior inguinal canal wall is otherwise intact.

The common direct inguinal hernia, on the other hand, is larger and reduces with ease. The external ring is dilated. The transmitted impulse on coughing is strong. After reduction, one can pass the examining finger through the enlarged external ring and feel the lack of substance in the posterior inguinal canal wall lateral to the arching fibers of the conjoined tendon. Frequently the superior ramus of the pubis can be felt through the frayed-out posterior inguinal canal wall.

Even though the supravesical hernia occurs mainly in the older age groups, nevertheless, the prognosis following repair is excellent, being perhaps as good as that of indirect inguinal hernias. For this reason, if there are no contraindications, surgical repair should be advised.

Why should this type of direct hernia have a different prognosis from the usual one? The main reasons appear to be: that the defect in the conjoined tendon, even in larger hernias, is relatively small; that the tissues are of excellent tensile strength and thus can hold a suture well; and, particularly, that the edges of the ring are capable of being approximated easily and without any tension. Furthermore, since the defects in the tendon are oval in outline, with the greater diameter of the oval parallel with the fibers of the tendon, contraction of the inguinal falx tends to approximate the edges of the defect. This in turn would reduce tension on the suture line, promote healing, and prevent the sutures from cutting.

Although we interposed the aponeurosis of the external oblique between the sutured hernial ring and the spermatic cord for purposes of reinforcement, it is not entirely certain whether this step in the repair is essential. It is likely that excision of the sac and closure of the ring alone would be sufficient to produce the excellent results that were achieved.

With regard to the foregoing aspect of the repair, there were 5 patients, among the 16 with previous hernioplasties, who had previous subcutaneous transplantations of the cord. We assume, in these cases, that the inferior part of the inguinal canals were thoroughly inspected because the cords would have to be completely mobilized in order to suture the external obliques behind them. Despite the fact that 5 cases are of no statistical significance, the presence of the external oblique aponeurosis immediately adjacent to the conjoined tendon did not prevent the occurrence of a defect in the latter. Therefore, one might argue that in the repair of the type of hernia we are discussing, the use of the external oblique as a reinforcing layer is not essential. Nevertheless, we have continued this part of the procedure in the manner described on the ground that it would do no harm and might be valuable.

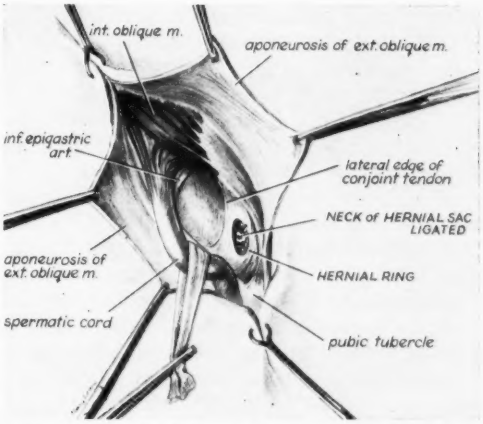

Fig. 3. View of right inguinal canal after the hernial sac and its coverings have been resected. The hernial ring is in the conjoint tendon, a short distance superior and slightly lateral to the pubic tubercle. The long axis of the oval defect is parallel with the fibers of the conjoint tendon.

In the 11 other patients with recurrent hernia, the spermatic cord had been replaced within the inguinal canal. At reoperation, in several of these cases, the spermatic cord and supravesical hernial mass appeared to be in virgin territory inasmuch as they were singularly free of adhesions to the surrounding tissue in the lower portion of the inguinal canal. Indeed, the dissection of the hernial mass was as easy in these cases as in those patients who had never been operated upon before. We suspect that the supravesical hernia existed

unrecognized in these patients at the time of previous operation, being perhaps of smaller size. This suspicion gives additional weight to the importance of freeing completely the entire length of the spermatic cord in order to examine the lower part of the posterior inguinal canal wall.

There were 10 patients in whom, at operation, an indirect hernia was discovered in addition to the supravesical hernia. Seven of these were small and were not the hernias noted by the patient and found on examination. In 3 patients, the indirect hernia was the one observed clinically and the supravesical hernia was small and an incidental finding. In these patients there was a small defect in the tendon with protrusion of a mass of extraperitoneal fat. These 3 were the only patients in whom no sac was found in the fat.

In dissecting the sacs of the supravesical hernia in the first 7 of this latter group, it was found that the small indirect hernias could not be converted into the larger ones or vice versa. This finding is quite contrary to the easy mutual convertibility of either sac into the other in the usual pantaloon or saddlebag type of direct-indirect hernia. The probable explanation of this difficulty of convertibility lies both in the increased distance separating the hernial sacs as compared with the short distance separating the sacs in the pantaloon variety and in the fact that the intervening anterior parietal peritoneum has normal tissue tension and elasticity rather than being completely lax as in the cases of easy convertibility. In the latter type of hernia, only the inferior epigastric vessels separate the direct and indirect sacs. The findings of inconvertibility in these 7 cases is strengthened by those in the 2 patients who developed small indirect ingiunal hernias in the immediate postoperative phase. We have, therefore, adopted the policy of exploring the spermatic cord in every instance, after the defect in the conjoined tendon has been sutured.

The etiology is not entirely clear. The portion of the conjoined tendon which is derived from the internal oblique is inserted into the pubic crest and has no insertion into the superior ramus of the pubis lateral to the pubic tubercle. Only the transversus abdominis gains insertion into the superior ramus of the pubis. Since the defect in the tendon is immediately superior or superolateral to the tubercle, it would seem clear that the fault occurred only in the transversus abdominis. At this level one can postulate an area of relative weakness in the conjoined tendon where the transversus changes direction and loses the reinforcement of the overlying layer of internal oblique.

In addition, the abundance of fat in the hernial mass is impressive. If one combines this factor of local obesity with a point of weakness or divergency of muscle fibers which are losing one layer (the internal oblique), one may develop a theory as to the etiology of this hernia. The factor of age may have an added effect.

CONCLUSIONS

1. Hernias of the supravesical fossa presenting through the conjoined tendon are more common than is generally realized.

2. They often present distinct physical signs so that a clinical diagnosis is possible before operation.

3. These hernias occur primarily in the older age groups, being present mainly in patients over 40.

4. The prognosis after repair is excellent.

5. Indirect inguinal hernias, when present concomitantly with the supravesical hernia, are not readily convertible.

6. Factors of age and local obesity probably contribute to the development of the defect in the conjoined tendon in an area where the latter consists only of the transversus abdominis.

7. Failure of recognition of a small supravesical hernia during the repair of an indirect inguinal hernia may account for a proportion of direct recurrences, particularly those that appear at the lower angle of the surgical scar. This emphasizes the necessity of freeing the spermatic cord over the full length of the inguinal canal in every hernioplasty performed upon a patient over 20 years of age, so that the entire posterior canal wall can be inspected.

THE MANAGEMENT OF URINARY FISTULAS IN A PRIMITIVE POPULATION

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IN primitive populations in Africa there is a high incidence of vesicovaginal fistula. It would appear that this has existed from the earliest times. There is no evidence to suggest that so far its frequency has been greatly diminished by improving social conditions and medical services. Taking British West Africa as an example, it is a rarity to find any major hospital in which there is not at least 1 case of vesicovaginal fistula under treatment, and in a few specialized centers, as many as 5 or 6 patients may be under treatment at any one time.

This condition is well known as among the most miserable requiring treatment by the gynecologist. The African woman, though not especially fastidious, finds it as distressing as would a European patient similarly afflicted. It is possible indeed that her sorrows are even greater in view of the extremely crowded social conditions in the majority of African villages.

The situation is further complicated by the superstitious importance attached to the reproductive function in a community comparatively close to the pagan, together with the alarm with which signs or symptoms referable to the genital tract are viewed. The relationship of female physiology to the cult of witchcraft is a particularly close one.

Fistulas are frequently multiple. For example, it is quite common to discover a vesicovaginal fistula in a person who also has a rectovaginal fistula with or without complete perineal tear. This not only increases the disability, but adds to the problem of operative treatment.

Between December 1948 and June 1952, while in Nigeria, I saw and personally treated 48 cases of urinary fistula, 3 of which were complicated by concurrent rectovaginal fistulas.

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ETIOLOGY

The most common etiologic factor was childbirth. Cases were also seen after operative treatment, which in 1 case had been carried out at the hands of the witch doctor. Disease contributed, but it was not numerically speaking an important factor. There was a complete absence of postirradiation fistulas, since as yet there are no facilities for radiotherapy in Nigeria.

The distribution of these cases was as follows: 41 cases (85 per cent) following childbirth, 5 after operative trauma, and 2 in which disease was the etiologic factor.

In the cases in which childbirth was implicated, it was usual to obtain a history of delayed labor. Details of the precise cause of dystocia were rarely available. In the 9 cases in which it was possible to observe the development of the fistula, the most important factor was prolonged or exceptionally severe pressure by the presenting part on the anterior wall of a genital tract in relation to which there was unrelieved distention of the bladder (Fig. 1). In this group 27 developed a urinary fistula as a result of the first confinement, and 3 of them had concurrent rectovaginal fistulas. Thirteen of these primiparas were between the age of 15 and 20 years inclusive.

In the 5 cases in which operative trauma was responsible for the fistula, the operative details were available. Previous total hysterectomy was the cause in 1 case, and in 2 cases a pelvic floor repair one of which was a sling type of operation for stress incontinence. In the fourth case a plastic operation for the relief of vaginal stenosis caused a vesicovaginal fistula. In the fifth case a witch doctor had incised the hymen and the whole length of the urethra and bladder neck when passing a cutting instrument for the relief of dyspareunia in a young girl aged 20 (Fig. 2).

Fig. 1. Distention of the bladder on admission in a case of delayed labor.

Disease was the etiologic factor on 2 occasions. In one case the incontinence developed as a result of carcinoma of the cervix spreading to the bladder and in the other, as a result of lymphogranuloma inguinale. The latter condition as a cause of urinary fistulas has previously been described by Gray.

TYPES OF FISTULA

A urethrovaginal fistula was found in 1 case, being the result of childbirth.

In 38 cases of urethrovesicovaginal fistula (79 per cent of the entire series), 35 followed childbirth, 2 followed operative trauma, and 1 was the result of disease (lymphogranuloma inguinale). In these cases the vesical end of the urethra was absent for a variable distance, and likewise there was a varying deficiency at the bladder neck. The majority of cases were very severe; in the worst there was complete absence of the urethra with a bladder deficiency of 1½ inches in diameter revealing pouting mucosa and, in 2 cases, the ureteric orifices also. These 2 cases will be described in detail in the section on treatment by vaginal operation. It was in this group that there were 3 cases of concurrent rectovaginal fistula.

Vesicovaginal fistula was found in 9 cases, varying in size from ⅓ to ¾ inch in diameter, as the result of previous operation on 3 occasions and of disease (carcinoma of the cervix) in 1 case. Some fibrosis was present but, in all except 1 case, there was no marked deficiency of tissue.

MANAGEMENT

The first principle was to make a decision whether or not to attempt to close the fistula by vaginal operation. This decision made, the patients required preliminary treatment to eliminate urinary tract infections and local skin infections. The majority of patients also required treatment to eradicate chronic malaria and varying worm infestations.

In 8 of the 9 cases of vesicovaginal fistula and the 1 case of urethrovaginal fistula repair was performed per vaginam. The ninth vesicovaginal fistula was due to carcinoma of the cervix, and in this case the ureters were transplanted.

While fistulas of all types presented their various difficulties, these were greatest in respect of the urethrovesicovaginal group. In them there was frequently marked deficiency of tissue which alone did not prevent successful closure by the vaginal route. In 22 of the 38 cases in this group closure was effected per vaginam, some degree of urethral reconstruction being necessary in addition to repair of the bladder. In deciding to attempt vaginal closure, no case was refused merely on account of the size of the fistula. If the tissues in its neighborhood were judged adequate the attempt was made. Furthermore, no patient was denied vaginal operation in the belief that subsequent urinary continence might be incomplete. In fact, closure was accomplished in these 22 cases of urethrovesicovaginal fistula in the face of this risk. In 4 of them residual stress incontinence was treated by secondary operation in the form of a Kelly type plication.

In the other 16 patients with urethrovesicovaginal fistulas, 3 of whom also had a rectovaginal fistula, ureteric transplantation was carried out as an elective procedure in 14. In 2 others it was resorted to when previous attempt at vaginal closure had failed.

In making the decision not to attempt vaginal closure, the following points were considered:

1. Exceptional difficulty of access. In a number of cases stenosis of the vagina was such as to make vaginal closure out of the question. This stenosis was believed to be produced by vaginal application of caustic native medicaments to overcome delay in labor.

2. Exceptional fixation of tissues. In some cases in which access to the fistula was not

obstructed, there was exceptional fixation of the paravaginal and paravesical tissue to the bony pelvis. In these cases it was thought improbable that any approximation of the tissues could be obtained even with the aid of relief incisions. The degree of such fixation was not directly related to the size of the fistula. In some fistulas where the gap was so large as to allow inversion of the bladder into the vagina, the surrounding cellular tissues were still sufficiently elastic to permit movement. Conversely, dense fibrosis resulted in complete fixation of some small fistulas.

PRINCIPLES OF VAGINAL OPERATIONS

The incidence of urinary fistulas in the United Kingdom is such that the author had seen only 2 cases prior to his departure for Nigeria. Advice was sought from Professor J. Chassar Moir but the unavailability of silver wire in Nigeria at the commencement of this study compelled me to make certain departures from his advice, and Chinese twist silk was used. Meeting with success with the earlier cases, I continued to use it for all cases.

All cases judged operable per vaginam were repaired under spinal anesthesia with the patient in the prone Trendelenburg position. Undergraduate Africans or nurses maintained the position of the lower limbs. A two layer technique was employed, using varying sizes of Chinese twist. A fine gauge (No. 00) was used for the first layer, i.e. subepithelial bladder sutures, and a No. 2 for the vaginal skin. In all the severe cases mobilization was necessary, combined with relieving incisions. The saucerizing technique was used for the less severe cases. But where there was marked deficiency of vaginal skin the saucerization was minimal, and I preferred to undercut. Particularly did this apply where urethral reconstruction was necessary. This was found necessary in the 22 cases in which there was a urethrovesicovaginal fistula. As mentioned before, the majority of these cases were very severe and the repair technique is depicted in Figures 3 to 6.

Figure 3 shows a sagittal section of the preoperative condition. In Figures 4a and b traction sutures are shown in position in the vaginal skin around the fistula. These are of considerable assistance to bring the fistula within easier access. In order to ensure correct apposition and continuity it was often found helpful to incise the intact urethra and to lay it open as shown in Figures 4b and c. An added advantage of this latter procedure was that in long-standing cases that portion of the urethra was frequently stenosed at its vesical end.

Fig. 2. Urethrovesicovaginal fistula caused by a cutting instrument.

The next step was to undercut the vaginal skin from the muscle wall of the bladder and urethra, and this is shown in Figures 4d and e.

The first layer of stitches was then inserted. These were interrupted Lembert-like sutures, placed in the submucous tissues so as to invaginate the mucosa (Figs. 5a, b, and c). It was found advantageous to do this over a catheter or bladder sound so as not to constrict the urethra. In addition, these sutures were commenced superior to the fistula in order to tighten the bladder neck so as to obviate subsequent stress incontinence.

The vaginal skin was next brought together with interrupted mattress sutures (Figs. 5c and 6). The diagrams illustrate for reasons of clarity a case relatively uncomplicated by vaginal stenosis and fixation of tissues, and little absence of tissue. Such a case was the one depicted in Figure 2. But generally speaking much mobilization by undercutting and relieving incisions was neces-

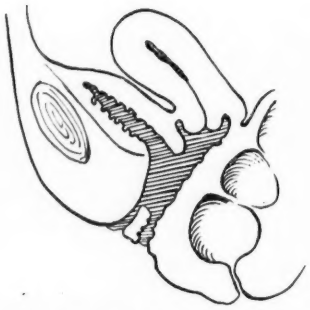

Fig. 3. Sagittal section in a case of urethrovesicovaginal fistula.

sary in order to close the lateral edges of the lesion in the bladder. It was often at these lateral edges that a subsequent breakdown occurred. A further difficulty arose during urethral reconstruction when, as a result of much tissue destruction, it appeared likely that some urethral stenosis might occur, especially as it was often necessary to use a particularly small catheter over which to insert the sutures. Despite this difficulty at no time was it necessary subsequently to dilate the repaired urethra.

Considerable oozing occurred at the time of making the relieving incisions and tended to obscure the field of operation. This difficulty was overcome by the use of a sucker, or small hot swabs, and occasionally small swabs soaked in 1/1000 adrenalin hydrochloride.

Difficulty of access could on occasion be quite satisfactorily overcome by the use of unilateral or bilateral Schuchardt incisions, which were repaired in the usual way after the fistula had been closed. The raw edges of the relieving incisions were not sutured, and oozing was controlled by the use of a vaginal pack for 12 hours, a duration of time found in the tropics to be less likely to favor infection than the 24 hours which one would have preferred. These raw areas subsequently healed by granulation.

Postoperatively, continuous drainage of the bladder, without suction, was carried out for 7 to 10 days. The catheter employed was a standard soft rubber one secured by suture. Self-retaining catheters were avoided for fear of damage to the deep suture line. The patients were nursed in the prone position, which was well tolerated. The vaginal sutures were removed on the twentieth day.

As a routine all patients had antitetanus serum preoperatively, and antimalarials and urinary antiseptics postoperatively. The bowels were confined until the catheter was removed. Thereafter, the patient was encouraged to micturate at half hourly intervals on the first day, hourly on the second day, and at increasing intervals until micturition was as normal as could be expected under the particular circumstances of each case. In most cases this was surprisingly satisfactory. In addition, as soon as the catheter had been removed, the patient was given perineal exercises. As mentioned previously, 4 of the 22 patients with a urethrovesicovaginal fistula had residual stress incontinence which was cured by a secondary operation in the form of a Kelly type plication. One of these 4 patients was the young girl whose fistula is shown in Figure 2. She subsequently became pregnant, and I performed a cesarean section at term.

SPECIAL CASES

There were 10 cases of urethrovesicovaginal fistula in which the bladder mucosa was pouting or partially inverted into the vagina. Of these, 2 cases deserve special mention. In them the fistula was so large that functioning ureteric orifices could be clearly seen.

Both cases appeared operable per vaginam and these patients were subjected to the standard operation described with the additional precaution of ureteric catheterization at the commencement of the operation. The ureteric catheters were brought out through the reconstructed urethra. It is thought that this precaution helped to prevent ureteric constriction during the repair and also tended to keep a large repaired area drier than might have been the case had transurethral drainage only been practiced.

In the first case the bladder deficiency admitted 3 fingers, and 7/8 inch of the vesical end of the urethra was absent. The ureteric catheters were passed a distance of 15 centimeters, and the repair was carried out over these in the usual way. There was, however, some deficiency of vaginal skin, and the first suture

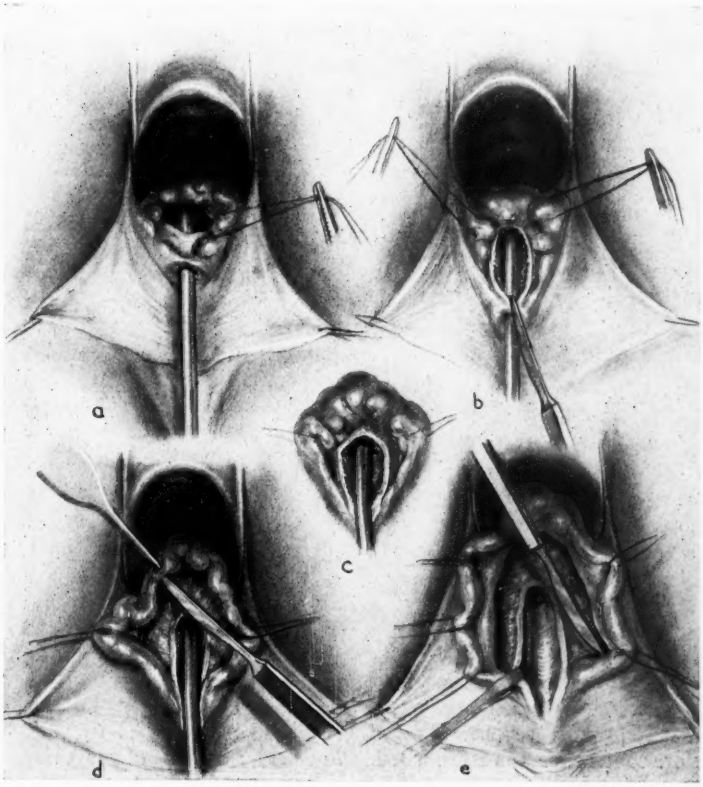

Fig. 4. Urethrovesicovaginal fistula. The stages of the repair are shown. The patient is in the prone Trendelenburg position.

line was reinforced by turning vaginal flaps over from the site of lateral longitudinal relieving incisions. The catheters were left in situ for 5 days, during which time they drained adequately. On the fifth day they were removed and replaced by a transurethral catheter because there was some leakage of urine around them. There was a small central breakdown of the repair, 1 by 0.1 centimeter, which required 2 subsequent repairs before the patient was continent. She failed to report for follow-up.

In the second case the defect in the bladder admitted 2 fingers, and the vesical half of the urethra was absent. Through this defect had prolapsed the trigone of the bladder including the interureteric ridge (Mercier's bar). The same procedure was followed in the repair in this case except that no vaginal flap was necessary since there was adequate vaginal skin. The right ureteric catheter became blocked on the fourth day and both were removed, being replaced by a transurethral catheter. This repair partially broke down and a further repair was successful 1 month later.

Results. At an early stage in this study one learned not to prognosticate too dogmatically. Some of the more severe bladder and urethral defects were closed and the patients cured when the chances appeared negligible. Conversely, some of the smaller fistulas caused most difficulty requiring several attempts at closure. It was thought that this was due to dense fibrosis, and more attention to mobilization and relieving incisions in these instances might have resulted in earlier success.

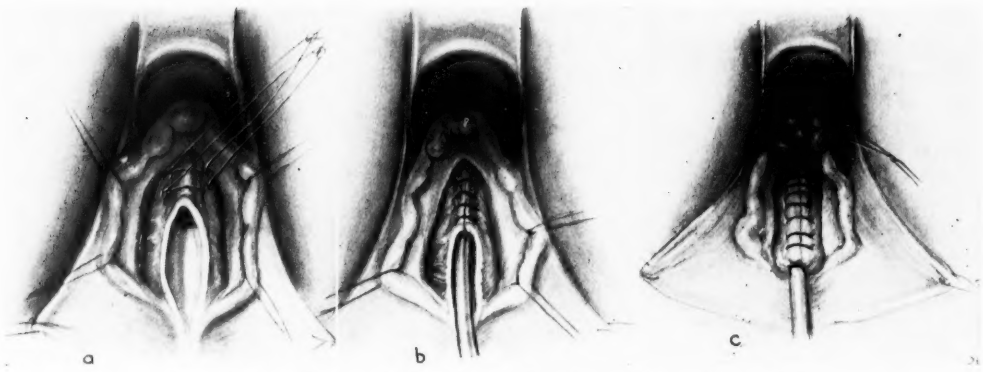

Fig. 5. Urethrovesicovaginal fistula. Further stages of the repair are shown.

In all, 31 cases were repaired per vaginam, a total of 58 operations (excluding the 4 plication operations) being necessary on these patients. Fifteen were cured by the first operation and another took her own discharge on the ninth day after the first operation, which appeared to have diminished the incontinence. Eight patients required 2 operations, and another died from cerebral malaria 2 days after the second operation. Four patients required 3 operations, and 1 required 4 attempts at repair. One patient required 8 repairs followed by plication before continence was established.

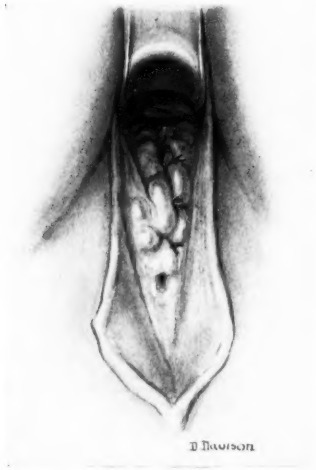

Fig. 6. Completion of operation for repair of urethrovesicovaginal fistula.

In addition to the patient who died from cerebral malaria, 1 other patient died from typhoid fever 3 weeks after being cured.

Many of the patients had travelled long distances to obtain treatment, and for some, in whom repair was not successful at the first attempt, it meant a long stay in the hospital. Without exception they readily submitted themselves to repeat operations, encouraged by the success obtained on their more fortunate sisters. As a result of the long distances travelled by many of these patients, the follow-up by me was of short duration, but they were in touch with their own doctors.

URETERIC TRANSPLANTATION

Seventeen cases judged inoperable per vaginam were submitted to ureterosigmoid anastomosis as an elective procedure. By reference to Table I, it will be seen that 1 of these patients had a vesicovaginal fistula due to disease (carcinoma of the cervix), and that 16 had a urethrovesicovaginal fistula. Of the latter, 14 were the result of childbirth, 1 the result of operative trauma, and 1 due to disease (lymphogranuloma inguinale).

Preoperative treatment. The usual preliminary treatment to eliminate urinary tract infections, chronic malaria, and worm infestations was carried out. Three days prior to operation an aperient was given, followed by bowel washouts on the next 2 days. In addition the patient was given a low residue, mainly fluid diet. The latter, however, was not easy

to supervise throughout the 24 hours. Two days' preoperative treatment of sulfaguanidine or thalazole, and streptomycin was given; and also antitetanus serum on the morning of the operation, because of the local danger of tetanus as described by Jelliffe, Walker, and Matthews.

Operative technique. On the first 3 patients a two stage transplantation was performed. The Nigerian female patient does not willingly submit herself to abdominal section, in complete contrast to the way in which she willingly undergoes vaginal operations. As a result, the operation was performed subsequently in one stage on 14 patients. A Mayo's urine catgut guide was occasionally used, and the left ureter was usually anastomosed to the bowel above the site of the right-sided implantation. Ureteric catheters were not used except in 1 case of special interest, which will be mentioned later.

Postoperative treatment. A rectal tube was not used as a routine until after I had had 1 case of anuria which will be described in the following (Case 1). With the exception of this case, drainage and control of urine per rectum were established satisfactorily within 24 hours. Antimalarials, sulfaguanidine or thalazole, and streptomycin were continued for a further 5 days. The patients readily adapted themselves to their new mode of life, and they were encouraged to continue with pelvic floor exercises after their discharge from hospital.

CASES OF SPECIAL INTEREST

CASE 1. The patient, aged 36 years, para 5, had had incontinence of urine for 1 year, commencing 3 days after the fifth confinement, which had been of 3 days' duration and which had resulted in a stillbirth. On vaginal examination a very large urethrovesicovaginal fistula was found. This admitted 3 fingers; there was gross absence of tissue, and the pubic periosteum was palpable. The visual field was poor and the case was judged inoperable per vaginam.

A bilateral ureteric transplantation was performed under spinal anesthesia on March 27, 1952. Subsequently, there was complete anuria for 6 days, during which time the blood urea rose to 340 milligrams per cent. The right kidney became palpable, and there was bilateral renal tenderness.

On April 2, 1952, I decided to reopen the abdomen under spinal anesthesia. There were a few fine adhesions, but there was no real difficulty in unpicking the ureterosigmoid anastomosis on the right side.

Fig. 7. An intravenous pyelogram 28 days after retransplantation showing normal renal function.

When this was completed, it was found that the free end of the ureter was totally blocked by a blood clot the size of a pea. It was easily separated with instantaneous escape of a considerable amount of urine. In order to ensure drainage a ureteric catheter was passed superiorly for a distance of 3 inches, the remainder being passed inferiorly into the bowel lumen toward the rectum. The right ureterosigmoid anastomosis was then reconstituted. Contrary to current opinion, as expressed by Ashton Miller, it was thought possible that the blockage of the right ureter was causing reflex suppression of urine from the left kidney, and, since the patient was far from being a good operative risk, the abdomen was closed without disturbance of the left ureterosigmoid anastomosis. A rectal tube was passed for 48 hours, and drainage of urine commenced immediately. On the subsequent day the patient developed paralytic ileus, which necessitated gastric suction and intravenous fluids for 48 hours. Thereafter, progress was uneventful. The ureteric catheter was removed per rectum on the eighth day. An intravenous pyelogram was performed on April 30, 1952, 28 days after the retransplantation. This showed normal renal function on both sides (Fig. 7). The blood urea was also normal.

CASE 2. The patient, a Yoruba, aged 36 years, reported at the gynecologic clinic on September 15,

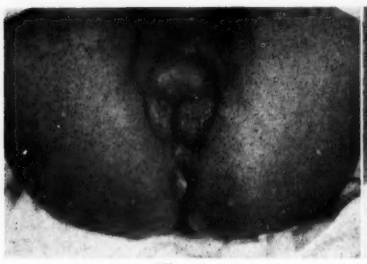

Fig. 8.

Fig. 9.

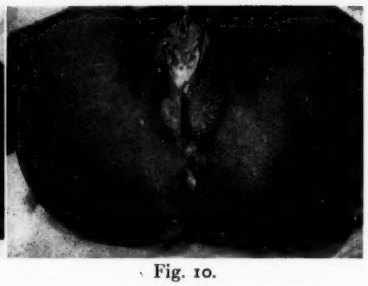

Fig. 10.

Figs. 8, 9, and 10. Elephantiasis of the vulva in a case of lymphogranuloma inguinale causing urinary fistula.

1950, having travelled 350 miles by freight lorry. She complained of incontinence of urine and sterility, which had been present for 19 years, immediately following a 4 day labor at term in her own home. A stillborn infant had been delivered at this her first and only confinement. Thirteen years later at another hospital, she underwent 2 abdominal operations within 3 weeks of each other in order to cure the incontinence of urine. She stated that bilateral transplantation had been performed. Since then, however, she passed urine per rectum and was still incontinent per vaginam.

On examination under anesthesia a large urethrovesicovaginal fistula was found with much fibrosis. Urine was seen to be passing from the bladder into the vagina. On rectal examination, urine was also found, and there was no rectovaginal fistula. There was only 1 abdominal scar.

It was considered that the patient might have taken her own discharge before the second transplantation had been performed, or that there was a double ureter present on one or both sides. It was not possible at this time to carry out an excretion pyelogram, nor was it possible to obtain previous operative details.

At laparotomy under spinal anesthesia on October 5, 1950, it was found that both ureters had been transplanted. On careful dissection on the right side, 2 further ureters were identified. An attempt was made to identify an abnormality of the right kidney, but this was not possible because of adhesions. The 3 ureters on the right were palpated to within 2 inches of the lower pole of the kidney. Three independent witnesses confirmed the findings of right-sided triple ureter. The 2 accessory ureters were transplanted separately in the usual way. No abnormality was found on the left side. Recovery was uneventful, and there was no further incontinence of urine per vaginam.

CASE 3. A nulliparous patient, a Hausa, aged 28 years, was first seen on September 14, 1951. She complained of vulval swelling for 10 years and incontinence of urine for 6 years. There was no history of trauma.

On examination there was elephantiasis of the vulva. Figures 8 to 10 show a preputial swelling, more marked on the left side, with chronic hypertrophic changes of the labia majora. The urethra was entirely absent, and there was a deficiency at the bladder neck which admitted 1 finger tip. On rectal examination there was some stenosis 1½ inches from the anus. The finger tip could be passed through this. There was a discrete inguinal gland on the right side which was removed for biopsy.

A diagnosis of lymphogranuloma inguinale was made. This form of lymphopathia venereum which appears to attack primarily the urethra has been described by Gray.

The progressive phase of the disease appeared to be past, but the patient was given a course of streptomycin prior to operative treatment. The destructive process had been so severe that the condition was considered inoperable per vaginam. A bilateral transplantation of ureters was performed, and the preputial mass was excised with the cautery. The patient made an uneventful recovery. Rectal con-

TABLE I.—RESULTS IN 48 PATIENTS WITH URINARY FISTULAS

	No. of cases	Etiology	No.	Repair		Results	
				Vaginal	Transplantation	Cured	Died
Vesicovaginal fistulas	9	Childbirth	5	5	—	5	—
		Operative trauma	3	3	—	2	1
		Disease	1	—	1	1	—
Urethrovaginal fistulas	1	Childbirth	1	1	—	1	—
Urethrovesicovaginal fistulas	38	Childbirth	35	21	14	33*	1
		Operative trauma	2	1	1	2	—
		Disease	1	—	1	1	—
Total	48		48	31	17	45*	2

*The 34th patient took her own discharge.

trol was good by day, but fluids had to be limited in the evenings in order to ensure nocturnal continence.

There were 3 patients with urinary fistula associated with rectovaginal fistula, all of whom had large inoperable urethrovesicovaginal fistulas, with large rectovaginal fistulas. In each case, the latter was successfully repaired prior to bilateral transplantation of the ureters, as a result of which the patients were continent. In 2 of these cases the deficiency of posterior vaginal skin was overcome by a flap operation which will be described in another publication.

There were 3 patients with urinary fistula associated with complete perineal tear, all of whom had inoperable urethrovesicovaginal fistulas. A perineorraphy was successfully performed in each case prior to bilateral transplantation of the ureters.

Results. Seventeen patients underwent transplantation of the ureters. Sixteen were discharged continent. The seventeenth died 2 days postoperatively from cerebral malaria.

SUMMARY

A series of 48 Nigerian patients with urinary fistulas is reviewed.

The etiology is discussed under the headings of childbirth, operative trauma, and disease. The most common etiologic factor was childbirth (85 per cent).

The types of fistulas are described. They were vesicovaginal, urethrovaginal, and urethrovesicovaginal. The latter was the most common (79 per cent), 6 of whom also had rectal damage.

The management is discussed and the reasons are given for the decision made as to whether to attempt vaginal repair or to perform a ureterosigmoid anastomosis.

In 31 cases a vaginal repair was performed, and the principles of the operation are described. A total of 58 operations was necessary on these patients before the fistulas were closed. In addition 4 patients required a subsequent plication operation in order to cure residual stress incontinence. Two cases of special interest are also described. In them there was marked prolapse of the bladder mucosa and ureteric orifices into the vagina. The ureteric orifices were safeguarded from constriction during and after the repair by the use of ureteric catheters.

Twenty-nine of these patients were cured. One took her own discharge and the other died from cerebral malaria on the second day after the second operation.

In 17 cases judged inoperable per vaginam, a ureterosigmoid anastomosis was performed. The preoperative and postoperative management and operative technique are described.

Cases of special interest are described. These were: retransplantation for anuria 6 days after bilateral ureterosigmoid anastomosis; a case of unilateral triple ureter; a case of lymphogranuloma inguinale as a cause of urinary fistula; and 6 cases of rectal damage requiring repair prior to transplantation. Sixteen of these patients were discharged continent. The seventeenth died 2 days postoperatively from cerebral malaria.

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MORPHOLOGIC AND PHYSIOLOGIC STUDIES ON THE GASTRIC REMNANT FOLLOWING RESECTION OF THE ESOPHAGOGASTRIC JUNCTION AND ESOPHAGOJEJUNOSTOMY

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NONNEOPLASTIC obstructing lesions near the esophagogastric junction associated with peptic ulcer, hiatus hernia, or cardiospasm with severe esophagitis and stenosis continue to present a difficult problem in management. Medical treatment is unsatisfactory as is mechanical dilation. It has been pointed out that esophagogastrostomy, subtotal gastric resection with or without vagectomy, the Heineke-Mikulicz type of cardioplasty, and the Finney type of plastic procedure performed at the esophagogastric junction may be followed by persistence of esophagitis and ulceration presumably due to reflux of gastric contents.

Yudin reported 80 cases of artificially constructed esophagi mostly for esophageal stricture secondary to the ingestion of caustics. He reviewed various surgical procedures for this and similar conditions. These procedures involve the substitution of a skin tube, colon, stomach, or jejunal segment for the strictured esophagus.

In 1946, Allison described a technique for partial esophagogastrectomy in Roux Y fashion for patients with chronic esophageal ulcers and stenosis associated with sliding hiatus hernia, and subsequently (3) mentioned that this procedure had been done in 15 of 63 patients so affected. More recently, he reported (4) that 23 patients with benign lesions at the esophagogastric junctions had been operated upon by this technique.

Barnes and McElwee reported 6 cases of nonneoplastic lesions at the esophagogastric junction surgically treated by resection of the distal esophagus including the vagus nerves and the proximal portion of the stomach with esophagojejunostomy in Roux Y fashion (Fig. 1). This procedure, similar to that described by Allison, accomplishes three things: (1) it removes the stenotic (or ulcerated) area; (2) it prevents or minimizes regurgitation of gastric contents into the remaining esophagus; and (3) it preserves a portion of stomach and so, perhaps, avoids the possible ill effects of a total gastrectomy.

The experiments described in this paper were performed to determine what, if any, morphologic or functional changes occur in the segment of stomach that remains after this procedure and whether esophagitis develops following this operation.

MATERIALS AND METHODS

Mongrel dogs weighing from 8 to 30 kilograms were prepared in the following manner: Under intravenous sodium pentobarbital anesthesia, an endotracheal tube was introduced and oxygen was administered at the rate of 10 liters per minute. A long left subcostal incision was made, and in order to accomplish resection of the esophagus the left pleural space was entered. The distal 2 centimeters of the esophagus and the proximal third of the stomach were excised and the remnant of stomach was closed. The jejunum was divided 20 centimeters from the ligament of Treitz and the distal stoma was anastomosed to the esophagus. The proximal jejunal stoma was next anastamosed to the jejunum in an end-to-side fashion at distances varying from 5 to 50 centimeters below the esophagojejunostomy (Fig. 1). The wound was closed in layers, and interrupted sutures of cotton or silk were used. Thirty-four dogs were so prepared.

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Aided by a grant from the Wyeth Foundation and Mrs. Percy Strauss.

In 9 of these dogs a flanged cannula was inserted into the stomach and brought out to the skin through a separate stab wound in order to withdraw specimens of gastric contents. In several dogs the cannula was inserted at a subsequent operation.

Control animals were prepared by inserting cannulas into the normal stomachs. In 3 animals the vagus nerves were divided, and the jejunum was divided at 20 centimeters from the ligament of Treitz. The distal end was then closed and the proximal end anastomosed end-to-side 5 centimeters distal to the closed end. Cannulas were inserted into 2 animals with vagus nerves intact. In 1 of these animals, the jejunum was divided and an end-to-side anastomosis was performed as described. In the second the cannula only was inserted.

During operation the dogs received an infusion of from 500 to 1,000 cubic centimeters of 5 per cent dextrose in water to which was usually added 250 milligrams of terramycin. Some of the dogs used in the early part of the study received 400,000 to 800,000 units of penicillin and 0.5 to 1.0 gram of dihydrostreptomycin intramuscularly in lieu of the terramycin. A few animals were given penicillin (400,000 units) and dihydrostreptomycin (0.5 gm.) on the first and second postoperative days. Nothing by mouth was allowed for 1 day after operation, then water was offered. On the third day after operation milk was added. By the fourth or fifth day the animals were on a full kennel diet consisting of dog biscuit, canned meat, and milk. Blood was drawn for determinations of hemoglobin and erythrocyte levels a few days before, and from 1 to 4 months after operation.

Biopsy or postmortem specimens of the esophagus and stomach were obtained on all animals. These specimens were fixed in 10 per cent formalin and stained in solutions of hematoxylin and eosin.

The dogs with intragastric cannulas were subjected to gastric analyses performed after fasting periods of from 12 to 16 hours. Samples were collected before histamine phosphate (0.2 mgm.) was injected subcutaneously and at 10, 20, and 30 minutes after the injection. The specimens were analyzed for free and total acid using 0.1 normal sodium hydroxide as neutralizer and titrating to the end point of Töpfer's reagent (free acid) and phenolphthalein (total acid). The results were calculated in clinical units.

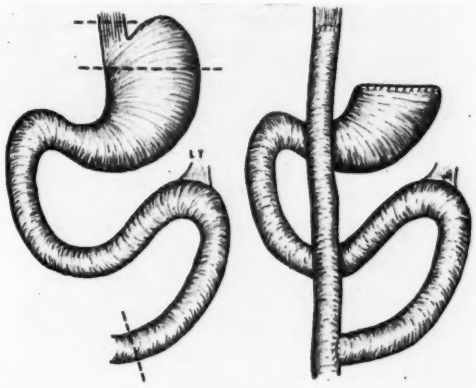


Fig. 1. Diagram of operation. The region of the esophagogastric junction is resected. The jejunum is divided 20 centimeters from the ligament of Treitz (*LT*) and esophagojejunostomy and jejunojejunostomy performed as indicated.

The average maximum response (A.M.R.) of free or total acid was calculated as follows: A.M.R. (in clinical units) equals the sum of the maximum responses for each dog multiplied by the number of determinations for each dog divided by the total number of determinations for all dogs:

$$\text{A.M.R. (Acidity)} = \Sigma \frac{\text{Maximum response (in clinical units) for each dog} \times \text{number of determinations for each dog}}{\text{Total number of determinations (all dogs)}}$$

Determinations of pepsin activity were carried out on the gastric juice of 5 dogs using the method of Mett as modified by Nirenstein and Schiff. Average maximum response of pepsin activity expressed in Mett units was calculated as follows: A.M.R. (Mett units) equals the sum of the maximum responses for each dog (expressed in Mett units) multiplied by the number of determinations for each dog divided by the total number of determinations for all dogs.

$$\text{A.M.R. (Pepsin activity)} = \Sigma \frac{\text{Maximum response (in Mett units) for each dog} \times \text{number of determinations for each dog}}{\text{Total number of determinations (all dogs)}}$$

Fig. 2. Roentgenogram made 60 days following the operation indicated in Figure 1. Barium introduced through the cannula revealed no abnormalities in size or shape of the remaining stomach.

At autopsy, histologic sections were made from the following organs: esophagus, esophagogastric or esophagojejunal junction, stomach, jejunum, liver, spleen, bone marrow, and lung.

RESULTS

Operative mortality. Thirty-four dogs were subjected to resection of the lower esophagus and proximal third of the stomach with esophagojejunostomy in Roux Y fashion. Seventeen dogs survived the procedure (50 per cent). Although the mortality figure is high, most of the deaths occurred early in the experimental period. As more experience was obtained, the mortality rate decreased markedly and at present is less than 10 per cent. The most frequent causes of death were peritonitis, leakage at the esophagojejunostomy, and pneumothorax. The death of 1 dog was due to bleeding at the site of closure of the stomach.

General. After recovery from the operation the dogs were alert, active, and had good appetites. They ate in their usual rapid fashion and after devouring about one-half of their ration would promptly regurgitate it. Despite this daily postprandial occurrence, none of the dogs learned to eat slowly or in small amounts.

Rapid passage of food through the intestinal tract was noted in most instances. Carmine red, fed to 4 animals, was eliminated in from 1½ to 4 hours. Several dogs with rapid elimination were noted to eat their stools which consisted essentially of the food they had just taken. Although rapid elimination was a common finding, diarrhea in the sense of watery bowel movements was unusual, occurring in but 3 animals.

The combination, however, of regurgitation and rapid elimination of ingested food led to conspicuous weight loss during the first few weeks after which the weight loss was gradual and slight. Usually a new weight level was reached which was then maintained.

The weight loss varied from 12 to 50 per cent with an average of 30 per cent in dogs studied during a 1 to 6 month period. One dog (No. 821) gained weight postoperatively.

Morphologic studies. The 17 dogs that survived the operation described underwent morphologic studies.

Gross appearance. Esophagus.—The esophageal mucosa was examined at autopsy in 16 dogs and by esophagoscopy in 1 dog (No. 887). In 16 dogs the esophageal mucosa showed no evidence of ulceration, erosion, or inflammation. In 1 dog (No. 967) in which the jejunojejunostomy was only 5 centimeters below the esophagojejunostomy, 2 shallow erosions about 2 millimeters in diameter were present in the mucosa close to the esophagojejunostomy. These did not penetrate the submucosa. Except for a small area of inflammatory reaction about these erosions, the mucosa was entirely unremarkable. There was no evidence of a stricture at the esophagojejunostomy or of dilatation of the esophagus, except in dog No. 922 in which the distal quarter of the esophagus was slightly dilated.

Stomach.—In all cases, the general shape, size, and thickness of the wall of the stomach remnant were unchanged from the appearance at the time of operation. While the usual rugae were present, there was usually flattening of the mucosal folds in the immediate vicinity of the flange of the cannula.

In 1 dog (No. 985), barium was introduced through the cannula to outline the size and shape of the by-passed stomach 60 days following operation. Roentgenographically the stomach in this animal was unremarkable (Fig. 2).

The upper gastrointestinal tract from 1 dog (No. 799), 116 days following operation, is representative of the gross appearance of the structures encountered at autopsy (Fig. 3).

Histologic appearance. Esophagus.—With the exception of dog No. 967 in which erosions of the mucosa were visible on gross examination, there was no evidence of esophagitis. The mucosa throughout was in no way different from that observed at operation. Healing at the site of esophagojejunostomy was good (Fig. 4).

Stomach.—The most striking change in the gastric mucosa following operation was the decrease in the number of zymogen granules present in the chief cells. The parietal cells stained more lightly than those in the specimens taken at time of operation but were otherwise unchanged. The total number of glandular elements seemed slightly reduced with a small increase of interglandular stroma (Fig. 5a, b). The lining mucous cells were in no way changed following the operation.

Other organs.—No significant difference could be noted in the bone marrow of control and experimental animals, and gross and microscopic examination of other organs (jejunum, liver, spleen, bone marrow, and lung) showed no variation from normal.

Blood studies.—In 8 dogs in which blood studies were made from 1 to 4 months after operation, a microcytic, hypochromic anemia developed. Hemoglobin values dropped an average of 16 per cent (8 to 24 per cent). In 1 dog the hemoglobin was found at the preoperative level 77 days after operation.

Physiologic studies.—Free and total acidity of gastric juice following histamine stimulation was determined in 9 experimental and in 5 control animals. In 3 of the control dogs, the vagus nerves had been sectioned. In every case there was an acid secretory response following the injection of histamine even as late as 203 days following operation (Table I). However, the experimental animals did not respond to histamine injections until 2 to 3 weeks after operation. Control animals in which no operative procedure other than insertion of the cannula had been done revealed the usual response to histamine as early as 1 week following operation.

Fig. 3. Organs from a dog sacrificed 116 days after the operation depicted in Figure 1. *S*, stomach; *E-J*, esophagojejunostomy; *J-J*, end-to-side jejunojejunostomy. The spleen can be seen adjacent to the stomach. A portion of pancreas lies to the left of the duodenum just distal to the pylorus.

In the experimental animals, the A.M.R. was 71 clinical units of free acid and 93 clinical units of total acid 20 to 30 minutes after the injection of histamine. In control dogs with the vagi severed, the A.M.R. (free acid) was 66 clinical units, and in those dogs with intact vagi, the figure was 110 clinical units (Table II).

Determinations of pepsin activity were made on 6 experimental and 5 control animals following the injection of histamine. In all cases the average maximum pepsin activity occurred in the fasting specimen or in that obtained 10 minutes after histamine was injected. Pepsin activity declined progressively in the specimens obtained more than 10 minutes after the injection. The average maximum response for the experimental animals was 89 Mett units. In control dogs with the vagi severed, the response was similar (81 Mett units). The control animals with vagus nerves intact had an average maximum re-

TABLE I.—ACID AND PEPSIN SECRETION IN EXPERIMENTAL AND CONTROL DOGS

Dog No.	Determinations No.	Days after op.	Average acid values after histamine: Free — Fast. spec.	Free — 10 min.	Free — 20 min.	Free — 30 min.	Total — Fast. spec.	Total — 10 min.	Total — 20 min.	Total — 30 min.	Pepsin activity (Mett units) after histamine — Fast. spec.	10 min.	20 min.	30 min.
Experimental														
871	3	199 201 203	12	61	89	83	51	105	107	119	176	144	116	73
875	1	50	8	9	30	17	30	32	45	40	—	—	—	—
887	3	186 189 191	31	65	86	100	55	90	111	126	71	27	26	20
922	4	63 76 111 113	10	34	45	72	51	62	75	95	31	27	26	20
948	4	30 46 84 86	4	16	61	71	20	49	75	89	18	—	34	27
962	2	26 39	15	41	73	69	50	61	97	89	—	—	—	—
967	2	19 29	15	24	76	81	62	40	88	93	—	—	—	—
968	2	15 25	4	Tr.	33	52	32	24	58	67	27	—	—	—
985	3	18 50 57	0	Tr.	36	43	19	27	60	67	82	112	106	66
Control														
1*	4	33 42 48 55	7	30	62	63	41	64	82	61	81	72	54	35
5*	1	21	—	10	7	10	—	40	36	43	—	117	100	83
6*	4	26 32 39 48	2	11	60	83	41	51	99	108	66	61	71	40
9	5	19 25 32 35 42	6	23	68	102	30	58	97	121	325	284	134	88
14	2	7 11	22	82	130	125	52	102	138	135	426	273	55	16

*Vagectomized.

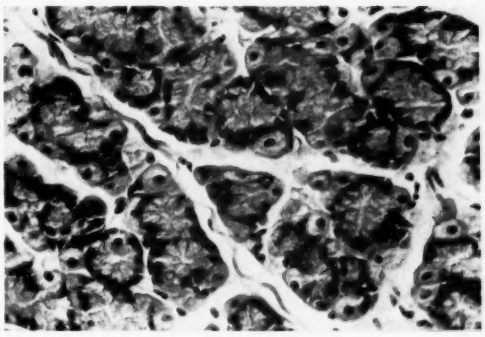
sponse of 354 Mett units (Tables I, II, and Fig. 6).

DISCUSSION

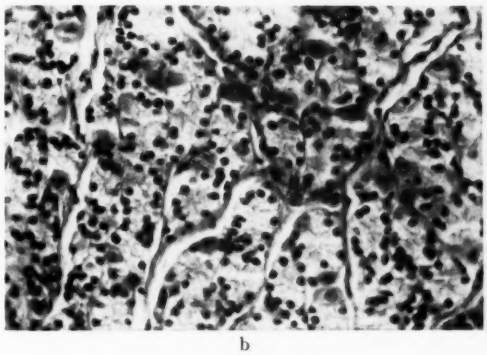
Following resection of the lower esophagus and proximal stomach with esophagojejunostomy in Roux Y fashion, dogs did not maintain their weight. This result is believed to be due to two factors: (1) frequent regurgitation of food; (2) rapid transit through the intestine with little chance for complete digestion and absorption. This may be remedied, at least in part, by frequent small feedings or by the formation of a jejunal pouch.

The studies described indicate that the portion of stomach that remains following this operation produces acid and pepsin although food has no access to it. It appears that under

Fig. 4.



a



b

Fig. 5.

Fig. 4. Photomicrograph of the healed esophagojejunal junction. There is no evidence of inflammation in the esophagus or jejunum.

Fig. 5. a, Microscopic appearance of gastric glands at time of operation.[1] Fine zymogen granules are evident in the cytoplasm of the chief cells. The parietal cells with centrally located nuclei have a more uniformly stained cytoplasm. ×195. b, Microscopic appearance of gastric glands 112 days after resection of the esophagogastric junction with esophagojejunostomy. Zymogen granules are inconspicuous in the chief cells. ×170.

these conditions gastric secretion is mediated only through the intestinal phase, since vagectomy destroys the cephalic phase, and diversion of food from the stomach by esophagojejunostomy eliminates the gastric phase. The average maximum responses of free and total acid and pepsin activity in the experimental animals were essentially the same as in animals with vagectomy alone (Table II). Free acid was reduced 35 per cent, total acid 26 per cent, and pepsin activity 75 per cent in the experimental and vagectomized control animals as compared with the nonvagectomized controls. Woodward and associates, in studies performed on dogs with a total gastric pouch, observed a reduction of from 18 to 82 per cent (average 49 per cent) in free acid, and a reduction of from 11 to 72 per cent (average 32 per cent) in pepsin activity after vagectomy. These studies were done on secretions from the pouch collected during a period of 24 hours and are not entirely comparable to ours, but the results are similar. Deaton and associates, who studied the response to histamine in dogs before and after vagectomy, following vagectomy found a reduction in free acid of 55 per cent and in total acid of 49 per cent (30 minutes after histamine). Dragstedt and co-workers similarly showed a decrease in free acid in the gastric juice of dogs with total gastric pouches following vagectomy.

In humans, Wood and his co-workers found that there was achlorhydria and low to absent pepsin activity in gastric juice from stomachs with severe atrophy of the mucosa. If normal or nearly normal appearing mucosa was present, secretions were usually normal or but moderately reduced. These observations agree with those of the present study where changes in the gastric mucosa were slight.

[1]The sections used in illustration were stained with hematoxylin and eosin. The magnifications stated are approximate.

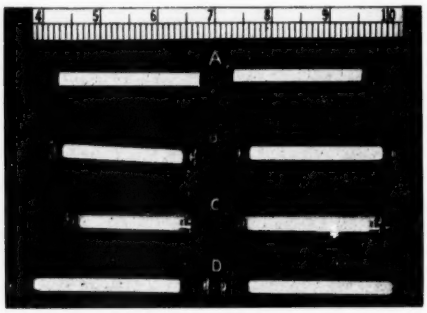


Fig. 6. Glass tubes containing albumin showing the effect of digestion with *A* hydrochloric acid (0.05 normal) alone; *B* gastric contents of experimental dogs (esophagojejunostomy with exclusion of stomach); *C* gastric contents of control dogs with vagi severed; *D* gastric contents of control dogs with vagi intact.

Mersheimer and associates found normally preserved mucosal cells in dogs at varying times following bilateral vagectomy alone or combined with partial gastric resection. In these experiments, however, there was access of food to the stomach. In the current investigation, food was not available to the stomach remnant, yet, in the absence of both cephalic and gastric phases of gastric secretion, morphologic changes in the cells of the mucosa were slight.

Table I shows that there is a decrease in pepsin activity following the injection of histamine in both the experimental and control animals. In 4 out of 5 experimental dogs there was initially a high response which occurred either in the fasting specimen or 10 minutes after injection. In subsequent specimens, however, pepsin activity fell. This is in contrast to the response of the acid following the injection of histamine where higher values were obtained in the 20 to 30 minute specimens than in the earlier samples. These findings are in accord with those of Alley.

TABLE II.—SUMMARY OF DATA ON ACID AND PEPSIN SECRETION IN EXPERIMENTAL AND CONTROL DOGS AS DETAILED IN TABLE I

	Experimental	Control	
		Vagectomized	Nonvagectomized
No. of animals	9	3	2
No. determinations	24	9	7
Average maximum response (A.M.R.) Free acid (clinical units)	71	66	110
Total acid (clinical units)	93	89	126
Pepsin activity (Mett units)	89*	81	354

*Results in 5 dogs

Topete and his co-workers reported that in 30 dogs subjected to esophagogastrostomy with the vagi intact, 27 developed peptic ulcer of the esophagus and 3 developed esophagitis. Following esophagogastrostomy with vagectomy, none of 20 dogs developed peptic ulcer of the esophagus and in only 1 dog was there esophagitis. According to these findings, it might be expected that vagectomy with or without esophagogastrostomy would be the procedure of choice in peptic ulcer of the esophagus. This has not been found to be the case in human patients.

While both acid and pepsin are produced in the remnant of stomach following the operation described, the possibility of the occurrence of esophagitis in these animals is minimized because of several factors. First, the amounts of acid and pepsin formed are low, comparable to those following vagectomy alone. Second, in passing from the remnant of stomach, the gastric juice is diluted and in part, at least, neutralized by the bile, pancreatic, and intestinal juices. Third, the segment of jejunum between the esophagus and the point of entrance of the gastric contents into the intestine (Fig. 1) provides a barrier through which the altered gastric juice must pass to reach the esophagus. In the experimental dogs, despite persistent postprandial regurgitation, only 1 dog (No. 967) developed esophagitis and erosion of the mucosa. In this animal the esophagojejunostomy was only 5 centimeters above the jejunojejunostomy through which gastric secretions entered the intestinal tract. Three other dogs with the jejunojejunostomy at 5 centimeters below the esophagojejunostomy did not develop esophagitis or ulcer, 1 as long as 252 days following operation. Since esophagitis and erosion occurred in 1 of 4 dogs with a short segment of jejunum between the esophagus and jejunojejunostomy, a relatively long segment of jejunum in this location is probably desirable. It has been shown by Brintnall, Daum, and

Womack that in Roux Y anastomosis of the jejunum, reflux does not occur if the limb of the Y is more than approximately 40 centimeters in length. Reflux can also be prevented in a shorter length of intestine by the construction of a valve as described by Perl.

While it is generally agreed that undesirable effects often follow total gastrectomy, there is some divergence of opinion concerning the results of excluding the stomach from direct continuity with the intestinal tract and so from contact with food.

Leven and Varco state, "theoretically and from experimental evidence there is somewhat greater likelihood of an ulceration occurring in the situation where the stomach is 'by-passed' than if continuity is made with the jejunum." Longmire has commented upon the importance of not by-passing the stomach in reconstructive operations involving the upper gastrointestinal tract.

Yet, Yudin with wide experience in reconstructive procedures on the esophagus says, "we have observed no disturbance in metabolism, in hermatopoiesis, or in growth or development in children" in which the stomach was excluded from direct continuity with the intestinal tract. Allison (4), who performed resection of the lower esophagus with esophagojejunostomy in Roux Y fashion with exclusion of the stomach in 27 patients with nonmalignant lesions, states that 19 were well in all respects, 2 died of tuberculosis 1 and 4 years after operation, 2 had anemia that responded to medical treatment, 1 had a dumping syndrome, and 3 patients had occasional diarrhea and discomfort after eating.

Our patients with nonmalignant lesions at or near the esophagogastric junction subjected to this procedure now number 11. We are still encouraged by the results, and a follow-up study will form the basis of a future report.

SUMMARY

1. Dogs were subjected to resection of the lower esophagus and proximal stomach with esophagojejunostomy in Roux Y fashion. Loss of weight was usually conspicuous in the postoperative period and appeared to be due to regurgitation of food and rapid passage of food through the intestinal tract.

2. Secretion of acid and pepsin in the stomach of the experimental dogs was similar to that in vagectomized control animals.

3. The gross and microscopic appearance of the remnant of stomach in the experimental dogs did not vary conspicuously from the controls. There was a moderate reduction in the number of chief cells and in the number of zymogen granules in their cytoplasm, with a slight increase of the interglandular stromal tissue. Bone marrow differed in no way from that in normal controls.

4. Esophagitis and superficial ulceration in the esophagus occurred in only 1 of 17 experimental animals. In that dog there were but 5 centimeters between the esophagojejunostomy and the jejunojejunostomy through which the combined gastric and pancreatic juice and bile entered the distal jejunum.

CONCLUSIONS

The portion of stomach that remains following resection of the lower esophagus and proximal stomach with esophagojejunostomy in Roux Y fashion produces acid and pepsin, indicating that cephalic and direct gastric stimuli are not necessary for the gastric mucosa to function. Morphologic changes in the gastric mucosa are slight.

Esophagitis following this procedure is rare and probably can be prevented by providing a long loop of jejunum (40 cm.) between the esophagojejunostomy and jejunojejunostomy.

These studies in dogs support the contention that this procedure may be of value in the management in humans of certain lesions at the esophagogastric junction by: (a) removing the obstruction, (b) preventing or minimizing regurgitation of gastric contents into the remaining esophagus and so diminishing the chance of occurrence of esophagitis, and (c) preserving a portion of the stomach and thereby perhaps avoiding some of the possible ill effects of a total gastrectomy.

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GAS INSUFFLATION THROUGH THE LUMBAR AND PRESACRAL ROUTES

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PERIRENAL insufflation through both the lumbar and presacral routes is now widely practiced in this country and abroad. Alone and combined with laminography, in many clinics it is an accepted method in the diagnosis of adrenal gland disorders and occasionally, renal disease. The time seems ripe for a mature evaluation of this technique and perhaps also for a word of caution on its application.

Over 30 years have elapsed since Rosenstein and Carelli and Sordelli almost simultaneously proposed the injection of gases into the perirenal fascial space for sharper differentiation of the renal shadow. This gave an area of increased contrast between the kidney shadow and the adjacent structures and permitted clearer visualization of the renal morphology. With improvement in the intensifying screens and with the advent of the Potter-Bucky diaphragm, the renal outline could be satisfactorily visualized on the simple film and, as a result, perirenal insufflation quickly fell into disuse.

The injection of gases into the perirenal space was revived by Cahill in order to delineate the adrenal shadow. This method was necessary because of the position, the small size, and the low physical density of the normal adrenal gland. It is now established that with the aid of the contrast provided by perirenal insufflation not only enlarged but at times normal adrenal glands may be clearly outlined.

As a further aid to the visualization of the adrenal gland, laminography (tomography, body-section radiography), which permits the delineation of structures at different levels, was first tried by me (13, 14) in 1937 and found practical and useful. The application of this combined method has proved of particular value in the sharper delineation of the normal adrenal gland and in the determination of the lesser enlargements (Figs. 1 and 2).

Gas can be injected directly into the perirenal fascial spaces through a needle inserted into the loin either by means of a hand syringe or pump or, better, by a slower low pressure technique with a 2 bottle pneumothorax apparatus as described by Mencher.

With the patient in the lateral kidney position a lumbar puncture needle is inserted immediately below the twelfth rib, just anterior to the sacrospinalis muscles. The needle is directed slightly upward through the subcutaneous fat, through the muscles, and finally through the transversalis fascia. When the needle reaches this fascia it meets a toughened resistance and then plunges suddenly into the soft perirenal fat layer. It is into this layer that the gas is injected. The sharp obturator of the needle is removed, but the blunt cannula part is left in situ. The cannula is inspected and aspirated in order to be certain that it has not entered a blood vessel. If any blood is withdrawn, the cannula is at once removed and a fresh attempt is made. Once the cannula has been properly inserted, from 250 to 500 cubic centimeters of filtered gas is slowly introduced with a 2 bottle pneumothorax apparatus. During the entire procedure the gas can be observed bubbling slowly through an inverted drip apparatus.

A new approach, presacral or retrorectal puncture, was recently described by Ruiz Rivas, whereby a needle is introduced at the level of the sacrococcygeal joint, 1 or 2 centimeters beyond the inferior border of the sacrum. The needle is directed obliquely upward, inward and forward so that its point comes to rest in the presacral or retrorectal space. A large amount of gas (800 to 1,250 c.c.) is usually injected rapidly in order to obtain an extensive retroperitoneal and mediastinal emphysema. This is commonly done with a large hand syringe with a 3 way stopcock.

From the Urological Surgical Service, Beth Israel Hospital, New York.

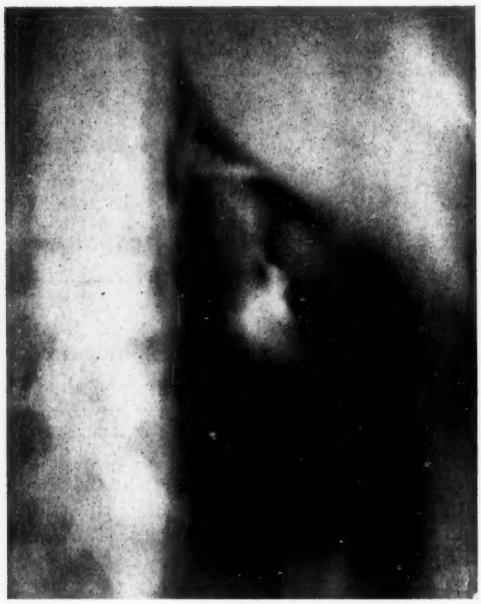

Fig. 1. Laminogram after lumbar insufflation and excretory urography, showing normal adrenal gland and kidney.

Fig. 2. Laminogram following insufflation, showing somewhat enlarged adrenal gland.

My associates and I have frequently been unsuccessful in attempts to produce adequate retroperitoneal emphysema with the pneumothorax apparatus or with a 2 bottle technique. It is evident that considerable pressure is required to inject gas in sufficient amount through the retrorectal space to visualize the far distant kidneys and adrenal glands.

Regardless of the approach, lumbar or presacral, the chief hazards of perirenal insufflation are: (1) gas embolism, (2) infection, (3) perforation of and injury to adjacent organs.

Gas embolism. Fish, Weyrauch, and others have recorded the occurrence of fatal gas embolism and serious reactions using hand syringe and bulb injection of gas into the loin. In 1939, A. Hyman and I reported a case in which, following the injection of 250 cubic centimeters of air with a hand syringe, the patient suddenly had a convulsion on the operating table, became unconscious, and stopped breathing. With artificial respiration and stimulants he began slowly to recover after 45 minutes. Since this vivid experience over 17 years ago, I have never injected air into the loin with a hand syringe or pressure bulb.

I did, however, perform well over 100 lumbar perirenal insufflations by means of a low pressure 2 bottle pneumothorax apparatus and have had the opportunity of observing many others done by staff associates and residents. This type of insufflation is time-consuming, taking from 30 minutes to well over an hour. There were no deaths or serious complications, and I consider the time well spent.

In the last 2½ years my associates and I have performed presacral retroperitoneal emphysema in 67 patients.

An elderly female patient, Beth Israel Hospital Case No. 264411, suddenly went into collapse on the operating table after 800 cubic centimeters of air had been injected into the presacral space with a hand syringe. Fifteen minutes later she was pronounced dead. On postmortem x-ray examination and at autopsy a large amount of air was found in the right heart chambers and in the larger and smaller veins.

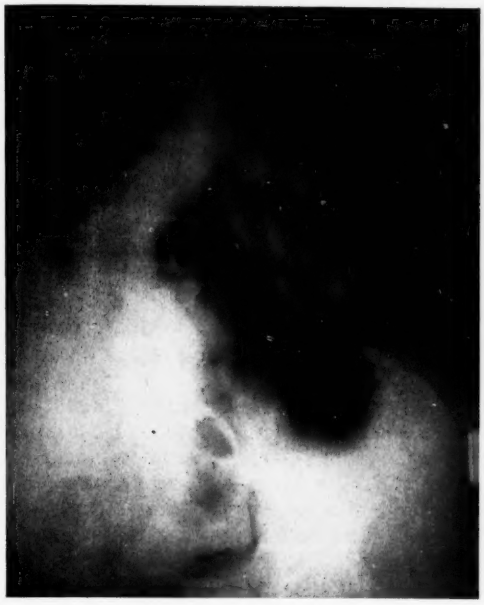

Fig. 3. Note gas outlining sigmoid and descending colon after perforation of rectum during presacral puncture.

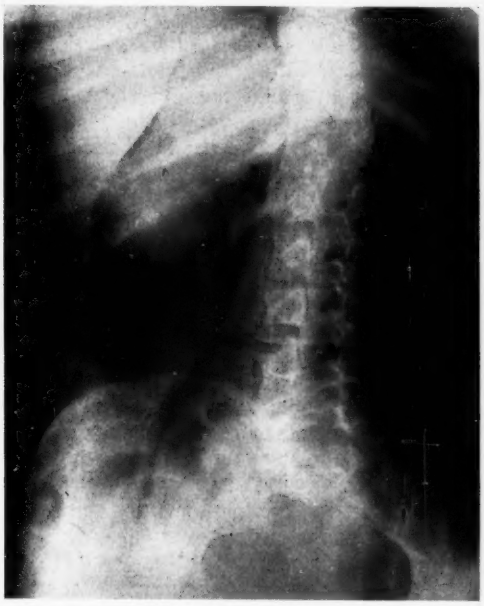

Fig. 4. Simple film following lumbar insufflation showing large adrenal tumor.

Another instance of gas embolism during presacral insufflation was reported by Russ and his co-workers. After the injection of 600 cubic centimeters of oxygen in about 15 minutes, their patient suddenly became cyanotic and went into collapse. A loud mill-wheel sound, evidence of gas in the heart, could be heard with each heart beat. The patient was in critical condition for about half an hour and then gradually recovered.

Durant, Long, and Oppenheimer have demonstrated that tremendous quantities of air can be injected intravenously in dogs without fatality if sufficient time is taken for the injection. A slow low pressure method is obviously safer than rapid hand syringe or bulb insufflation, for if the operator should inadvertently inject gas directly into the blood stream, there is usually an ample interval for warning signs. Any significant rise in pulse or respiratory rate, or any sudden discomfort or distress is reason for immediately discontinuing the insufflation.

Infection. Because of its close proximity to the rectum and anus, the presacral approach is more prone to bacterial contamination. An illustrative case occurred about 2 years ago in which presacral oxygen insufflation was followed within 36 hours by chills, high fever, and jaundice. At operation a large retroperitoneal phlegmon was found on the right side. Despite wide surgical drainage and the intensive use of antibiotics, this patient succumbed.

Keyes in 1923 reported acute suppurating nephritis following lumbar injection of oxygen.

We have had no infection in over 150 cases of lumbar insufflation and in 67 cases of presacral retroperitoneal emphysema performed at our hospital.

Injuries. With lumbar insufflation there is risk of inserting the needle too deeply so that it penetrates into the renal parenchyma or even into the peritoneum. Perforation of the kidney which occurred several times in our series was made apparent by the withdrawal of blood into the syringe. The needle was immediately removed and there was no apparent ill effect in these cases. In 1 patient a limited

parenchymal ecchymosis with a small subcapsular hematoma was found at operation a few days later.

With the presacral method there is real danger of injury and perforation of the rectum by the inserted needle. In fact, some operators advise insertion of a finger into the rectum in order to guide the needle. The possibility of serious infection and fistula following rectal trauma must be appreciated.

A stout middle-aged woman, Beth Israel Hospital Case No. 276135, during a presacral insufflation by an experienced urologist suddenly complained, "My stomach feels full." A simple film (Fig. 3) revealed excellent delineation of the sigmoid colon by the insufflated oxygen. Penicillin and streptomycin were promptly administered and there fortunately were no adverse effects.

Precautions. Certain precautions must be taken to minimize the inherent risks of lumbar and presacral insufflation:

1. The procedure must be done under strict aseptic conditions.

2. A blunt cannula-like needle with a sharp obturator should be used, for when the obturator is removed there is less likelihood for a blunt cannula to penetrate into a vein. The cannula is inspected and aspirated before any gas is injected. If blood is obtained, the cannula is immediately withdrawn.

3. The gas must be injected slowly under low pressure, preferably with a 2 bottle apparatus or by a syringe with exaggerated slow motion. The procedure should take from at least 30 minutes to an hour or more, depending on the amount of gas injected.

4. Whenever possible, the insufflation should be done with the patient in the left lateral position. Animal experiments and clinical experience indicate that gas does not accumulate in the right ventricle in this position but is propelled into the pulmonary circulation whence it is eliminated. In the right lateral position the gas is apt to form an air trap in the outflow tract of the right ventricle with fatal result. In the event of symptoms of air embolism, a patient should immediately be placed in the left lateral position.

5. A patient should be under constant observation throughout the entire procedure by a trained physician, preferably an anesthesiologist. A resuscitator and stimulants should be at hand.

Choice of gaseous medium. Oxygen was originally used by Rosenstein and carbon dioxide by Carelli. Since then oxygen and air have been more commonly employed. Oxygen is preferred by some in the belief that its quick absorbability makes it a safer medium in regard to gas embolism. Clinical experience, however, does not lend support to this supposition. Gas embolism is caused by sudden mechanical blockage of a large volume of gas bubbles in the right ventricle and its outflow tract.

Helium was tried in our hospital in the hope that this rapidly diffusible gas might improve the delineation of the kidneys and adrenal glands. I have come to the conclusion that the choice of gas makes little if any difference, either in the safety of the procedure or in the sharpness of the delineation.

Indications. It has by now been well established that perirenal insufflation either through the loin or through the presacral route is indicated in cases of suspected adrenal gland disease. The contrast provided by the injection of gases clearly visualizes enlargements and tumors (Fig. 4). At times, the normal adrenal gland may also be distinctly outlined especially in children and in thin individuals but this is the exception rather than the rule.

Laminography (tomography) when combined with perirenal insufflation has proved consistently superior in the delineation of the normal adrenal gland and its lesser enlargements as compared to the simple films after insufflation. The clear visualization of the adrenal glands by this method obviates the necessity for bilateral exploration.

Perirenal insufflation has a limited application in the diagnosis of renal neoplasm and in its differentiation from multiple renal cysts. When combined with pyelography and with aortography spectacular films may be obtained. Presacral retroperitoneal emphysema has been used successfully to outline other retroperitoneal tumors.

Lumbar versus presacral insufflation. Proponents of the presacral injection technique have almost universally stressed its innocu-

ousness as compared to lumbar insufflation. Duff and his co-workers have written the "method is easy to master and remarkably free from hazard."

The observations reported in this paper and those of others indicate that the presacral method is susceptible to the same dangers as direct insufflation into the loin. Air embolism has occurred with both techniques and can, I believe, be best prevented by using a slow low pressure method of insufflation.

Because of its close proximity to the rectum and anus, the presacral approach is more prone to bacterial contamination and infection.

The chief advantage of the presacral method is that both kidneys and adrenal glands are usually visualized with a single needle puncture. This technique, however, requires the injection of a large amount of gas (800 to 1,250 c.c.) and the creation of a massive retroperitoneal emphysema in order to reach up to the distant adrenal glands.

Direct lumbar insufflation, on the other hand, needs a smaller volume of gas (250 to 400 c.c.) and consequently a much more localized emphysema. This lesser procedure is preferable in many cases.

The contralateral side is not infrequently visualized after a single lumbar insufflation. When necessary, the opposite loin is injected, usually at a later date.

SUMMARY

In a review of over 150 cases of lumbar perirenal insufflation done with a slow low pressure 2 bottle pneumothorax apparatus, there have been no fatalities or serious complications.

More rapid hand syringe injection has resulted in 2 cases of gas embolism. One patient, injected with 800 cubic centimeters of air through the presacral route, died; the other, injected with 250 cubic centimeters of air directly into the loin, recovered.

The presacral injection technique is more prone to bacterial contamination and infection because of its proximity to the anus and rectum. A case of fatal infection and another of rectal perforation by the presacral method are reported.

Precautions necessary to lessen the inherent risks of gas insufflation are discussed.

Perirenal insufflation through the loin and through the presacral route is valuable in the diagnosis of adrenal gland disorders. It also has a limited application in outlining renal and other retroperitoneal tumors. Laminography, combined with perirenal insufflation, has proved consistently superior to insufflation alone in the delineation of the normal adrenal gland and its lesser enlargements.

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TOTAL AND ANTERIOR PELVIC EXENTERATION

I. Report of Results Based upon 315 Operations

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THE operations of total pelvic exenteration and anterior pelvic exenteration have been previously described (1, 2, 3). Such operations are indicated for advanced carcinoma in the pelvis in which more than one viscus is involved or are so close to involvement that their removal is indicated to encompass disease sufficiently in an attempt to achieve prolonged survival.

The operation of total pelvic exenteration consists of the en masse excision of bladder, lower ureters, vagina, uterus, adnexae, pelvic and lower sigmoid colon, and pelvic lymph node excision and removal of all pelvic peritoneum. The routine procedure is to implant the ureters into the sigmoid colon above the end colostomy, thus creating a wet colostomy (Fig. 1). In special situations the ureters are implanted into the skin, thus creating bilateral cutaneous ureterostomies. Substitute bladders using a segment of ileum were employed in only 2 instances.

The technique of ureterocolostomy employed has also been described in previous articles by the senior author. The same technique is followed whether the ureters are placed in the sigmoid to fashion a wet colostomy or into the intact colon.

The operation of anterior pelvic exenteration consists of en masse resection of bladder, lower ureters, vagina, uterus, adnexae, pelvic lymph nodes, and pelvic peritoneum. The pelvic colon is undisturbed and the ureters are implanted into it (Fig. 2). The patient does not have a ureterocolostomy and expels urine and feces per intact rectum.

The indications for anterior pelvic exenteration and for total pelvic exenteration depend upon the extent of visceral involvement. The operation of total pelvic exenteration with formation of wet colostomy was first carried out by one of us (A.B.) in December 1946 for involvement of all pelvic viscera by sloughing necrosis due to overintense reaction from radiation given in the treatment of cancer of the vagina. The indications for total exenteration, as stated, are involvement of all pelvic viscera by cancer or near involvement so that wide removal of disease can only be achieved by such an operation. The indication for anterior pelvic exenteration is apparent involvement of bladder, uterus, and vagina only, with the suggestion that the rectum is uninvolved and can therefore be preserved to avoid colostomy. This procedure, anterior pelvic exenteration with pelvic lymph node dissection in one stage, was first performed by one of us (A.B.) in December 1947 for carcinoma of a cervical stump invading the bladder, previously and ineffectively radiated, the patient being still alive without evidences of recurrence over 6 years later. In the male, pelvic exenteration consists of resection en masse of bladder, rectum, prostate, and pelvic node excision.

The radical nature of these operations, especially total pelvic exenteration, understandably, was and is regarded in some quarters as exceeding propriety, and opinion was (and is) expressed in some quarters that when cancer had progressed to the stage where such an operation was necessary to encompass its macroscopic extensions, the procedure was futile as recurrences and metastases would surely ensue. If such opinions were not so directly stated in the literature, nevertheless such was the inference in previous publications. The objectives envisaged in the earlier periods of experience with exenterations were merely palliative. All those who deal with advanced pelvic cancer, especially cancer of the cervix, are aware of the intense misery caused by such radiated and uncontrolled cancers. Since in many of these patients the

From the Memorial Center for Cancer and Allied Diseases, New York.

disease appears still localized to the pelvis it seemed that any procedure was worthy of trial to afford at least temporary relief. Re-radiation is so rarely successful after initial radiation failure that it is not to be recommended. However, some claim that 25 per cent or more recurrent cases may be salvaged by re-radiation for 3 to 5 years, but this is not the view of the large majority of leading radiation therapists.

The only test for the justification of pelvic exenteration operations is the results that might be achieved. Since it is now more than 7 years since the first total pelvic exenteration was performed and since approximately a hundred total and anterior exenterations were performed more than 5 years ago, a report of the results to date is in order and is partially summarized below. One of us (W.D.) reviewed in detail all the charts and codified them for record on "punch cards"; the various tabulations resulted from passage of the cards through the sorting machine.

MATERIAL

The patients in this series include those operated upon by the senior author, both ward and private patients, those operated upon by residents assisted by a staff member, including the authors, and private patients operated upon by various members of the attending staff on the service. Three patients operated upon by the senior author prior to his association with the Memorial Center are not included.

In Table I the primary lesions are listed together with the type of exenteration. It is noted that the most frequent lesion is carcinoma of the cervix, 225 patients; the next most frequent lesion is carcinoma of the corpus uteri, 22 patients; then carcinoma of the vulva, 18 patients; massive radiation necrosis, 15 patients; and then carcinoma of the rectum, 12 patients. In all 315 operations have been performed to December 31, 1953—202 total pelvic exenterations and 113 anterior pelvic exenterations. While in this series of patients the majority of lesions were gynecologic cancer, the general principles of surgical technique apply to bladder and rectal cancer as well.

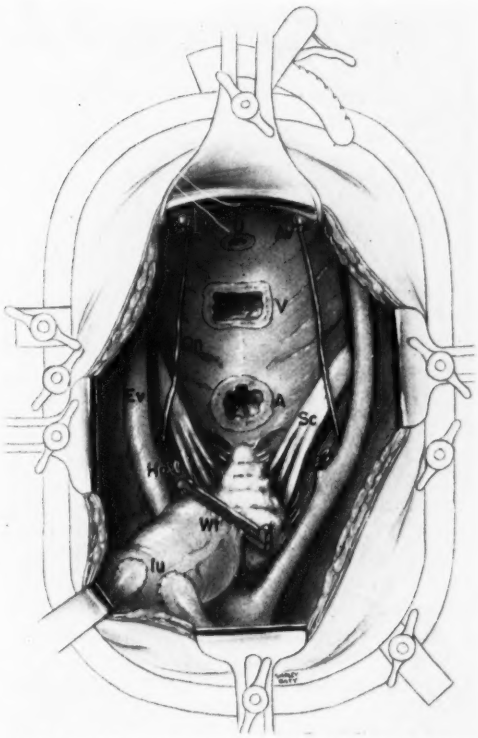

Fig. 1. Schematic representation of pelvis following total pelvic exenteration where all viscera, pelvic nodes, and peritoneum have been removed via the abdominal incision. The transected *U*, urethra, *V*, vagina, and *A*, anal colon, are depicted widely separated for illustrative purposes only. *Av*, ligated obturator vessels; *On*, obturator nerve; *Sc*, sacral plexus; *Hv*, ligated hypogastric vessels; *Ev*, external iliac artery and vein. *Wt*, end colostomy with *Iu*, ureters implanted above terminal opening. The Martel clamp is shown still in place on the colon.

Since bladder cancer gives rise to metastases earlier than gynecologic or rectal cancer, the results, if most of the cases were bladder cancer, would not be as good as are those reported herein.

SURGICAL MORTALITY

In computing mortality two criteria are employed. Immediate surgical mortality is defined as death within 30 days of operation from any cause. Patients dying for various reasons in the hospital after 30 days are regarded as hospital mortality. The total mortality is the sum of these two. In some

TABLE I.—ADVANCED LESIONS FOR WHICH EXENTERATION OPERATIONS WERE PERFORMED

(September 1947 to December 1953)

Primary lesion	Total exenterations	Anterior pelvic exenterations
Carcinoma of cervix	146	79
Carcinoma of corpus	11	11
Sarcoma of corpus	4	0
Mixed mesodermal tumor of uterus	0	1
Epidermoid carcinoma of vagina	6	1
Carcinoma of vulva	5	13
Melanoma of vulva	0	1
Embryonal adenocarcinoma of vagina	0	1
Carcinoma of ovary	5	1
Carcinoma of rectum	12	0
Rhabdomyoma of vagina	1	0
Massive radiation necrosis	12	3
Carcinoma of bladder	0	2
	202	113

Total No. of exenteration operations.....315

instances rapid recurrences developed, and the patients remained in the hospital and died several weeks after operation. There were 56 patients in this series of 315 who died within 30 days of operation, a surgical mortality rate of 17.7 per cent. This relatively high rate is due to the fact that since palliation, even brief, was envisaged in most of the series, selection of patients was minimal. A series of 19 consecutive total exenterations with 1 mortality was achieved during this period, and another consecutive series of 15 anterior exenterations with 1 mortality was also obtained. It is obvious that with varying degrees of selection lower surgical mortality figures would be possible. Among the 315 patients there were 28 who did not leave the hospital alive although surviving more than 30 days. This is a hospital mortality of 8.8 per cent. Thus, the total mortality is 26.6 per cent. One of 4 patients operated upon did not leave the hospital alive. There was a relationship between age of the patient and surgical mortality, as shown in Table II. The short survival among the 3 patients over 70 does not militate against operating upon patients in this age group. Since January 1, 1954, one of us (A.B.) has performed anterior exenteration in a patient 73 years of age for a large carcinoma of the cervix invading the bladder. Convalescence was uneventful, and she was discharged from the hospital in excellent general status and quite active physically. Obviously, however, advanced age increases the risk of mortality. It is interesting to note that the mortality among the age group 60 to 69 years is not greater than for the age group 50 to 59 years.

TABLE II.—SURGICAL MORTALITY IN RELATION TO AGE OF PATIENT IN EXENTERATION OPERATIONS

Age, years	No. patients operated upon	Per cent surgical mortality
1 yr.	1	0
20–29	6	0
30–39	41	7
40–49	111	16
50–59	100	22
60–69	52	23
70–80	4	25

The causes of immediate mortality are varied. There were 6 deaths in the operating room due to uncontrolled shock (blood loss), an incidence of 2 per cent. Four of these operating room deaths occurred in the last year —1953. The causes of immediate and hospital mortality are shown in Table III; for the most part they were poor risk patients whose operability ordinarily would be considered negative on the basis of poor general status combined with advanced disease. Shock, uremia, and complications of intestinal fistulas (usually in radiated bowel) accounted for 41 deaths among the immediate and later hospital mortality. It may be stated that the urinary tract was implicated directly in 13 of the 84 deaths, an incidence of 16 per cent in the series. Shock accounted for 12 deaths, an incidence of 15 per cent in the series of fatalities; otherwise stated, 4 per cent of all patients operated upon died of shock. Necropsy was done in 45 of the 84 fatalities and in 13 patients residual carcinoma was found. This is expected because in many instances palliation only was envisaged.

HEMORRHAGE AND BLOOD TRANSFUSIONS

Since the entire pelvis is denuded of peritoneum, areolar tissues, and lymphatics, large raw areas are created; these surfaces constantly ooze blood. This is controlled for the most part by packs dipped in hot saline solution. Also, denudation of the sciatic nerves

is of great importance because cancer of the cervix spreads to the fatty tissues over these nerves. The best method of denudation is the resection of hypogastric artery and vein and their branches. It is here that massive hemorrhage is apt to occur. Thus in carrying out the exenteration operations large quantities of blood should be on hand. The number of transfusions necessary greatly varies with the situations encountered.

In Table IV the number of transfusions are summarized among 314 patients. The 6 patients who died in the operating room are not included but the blood transfused was not beyond the maximal indicated. One infant received 250 cubic centimeters of whole blood. In the patient who was not included in the table, the records were faulty. The average blood transfused in all patients (314) was 3,500 cubic centimeters, 7 units. The extremes were ½ unit and 34 units. It is interesting to note that as the quantity of blood necessarily transfused increased, so did the surgical mortality. The latter was 10 per cent when 500 to 2,500 cubic centimeters were used, and 60 per cent when blood in excess of 16 units was necessary. It is not possible to predict how much blood will be lost in any given operation. Tissues may be edematous as a result of previous radiation therapy or there may be fibrosis; these factors contribute to reduction in blood loss. As indicated, blood loss occurs from oozing from the denuded surfaces. Severe hemorrhage may also occur from inadvertent opening of large vessels, especially the hypogastric vein and its branches. Another great danger of hemorrhage occurs in the excising of the hypogastric vein and its branches. Some of the latter (gluteal branches) may escape the clamps and retract between and behind the nerve branches of the sacral plexus. Since there is only soft tissue behind these nerve trunks as they course out of the pelvis through the sciatic notch, they cannot be easily secured with hemostats as there is no firm wall against which pressure can be exerted. During attempts to find and clamp them additional blood will be lost, and if these attempts persist for any period of time such blood will have been lost. Experience has indicated that

Fig. 2. Schematic representation of pelvis following anterior partial pelvic exenteration. Bladder, lower ureters, vagina, and uterus have been excised en masse, and ureters have been implanted into pelvic colon. Sacral plexus on both sides has been denuded.

firm packing with pads which have been soaked in hot saline solution is the preferred method for dealing with a situation of this nature.

LATE RESULTS

In Table V the "5 year" results are summarized. Actually these are 4 to 6½ year survivors. The incidence is 12 (12 per cent) of 104 patients. Table VI summarizes the patients operated upon in 1950 to 1951, i.e., approximately 2 to 4 year survivors; the incidence of survival is 30 per cent. The latter figure at this writing is interpreted as indicating the incidence of effective palliation by survival for at least 2 years in the group of 89 patients who were operated upon in 1950 to 1951.

TABLE III.—CAUSES OF SURGICAL AND HOSPITAL MORTALITY IN TOTAL AND ANTERIOR PARTIAL PELVIC EXENTERATIONS

Cause	Surgical mortality, dead in 1-30 days	Died in hospital 1-6 mos. postop.
Shock	12	0
Uremia	8	5
Intestinal fistula	6	10
Peritonitis	6	3
General sepsis	7	2
Cardiovascular	2	0
Cerebrovascular accident	3	1
Pneumonia	1	1
Cachexia	0	1
Embolism	2	0
Hepatitis	1	0
Hemorrhage, late	2	0
Undetermined	5	5
Infarcted intestine	1	0
Totals	56 (18%)	28 (9%)

COMPLICATIONS DURING LONG SURVIVAL PERIOD

Following the type of surgery represented by the exenteration operations all manner of complications are observed on occasion. However, no one type of complication has been observed much more frequently than others and should therefore be especially noted. Hyperchloremic acidosis has been observed, is easily controlled, and has not constituted a major problem. This is noted among those patients who received anterior pelvic exenteration, i.e., ureters implanted into the intact colon. The presence of the anal sphincter mechanism results in urine retention in the colon especially at night. In patients who exhibit these electrolyte imbalances, the recommendation is made to insert a rectal tube at night, and ingest large quantities of water during the day with soda bicarbonate at intervals. Attacks of ascending pyelitis occur and are treated by hospitalization and chemotherapy. Repeated, severe and uncontrolled attacks of ascending urinary tract infection have not been observed. Indeed, in the large majority of patients urinary tract infection has not been manifested. The incidence of pyelitis or other later complications has never been such as to raise, at any time during the past 7 years, the question of the compatibility of the operations with indefinite survival.

TABLE IV.—SUMMARY OF BLOOD TRANSFUSIONS EMPLOYED IN EXENTERATION OPERATIONS

No. of units 500 c.c. per unit)	No. of patients		Per cent surgical mortality in series
½ to 5	129		10
6 to 10	119		22
11 to 15	49		17
16 to 20	6		
21 to 25	6	17	59
27 to 30	4		
31 to 34	1		
Total	314*		

*One record excluded because of incompleteness.

Intestinal obstruction due to adhesions formed in the deperitonealized pelvis has not been a frequent problem. Intestinal obstruction has occurred at varying intervals after operation, but in almost all instances was found to be the result of recurrent or metastatic carcinoma. Obstruction due to adhesions has been encountered in 5 instances, but such adhesions were usually in the upper abdomen or to the ligated infundibulopelvic ligament. In 1 instance there was torsion of the small bowel about an adhesion formed to the site of a ureterocolostomy. In 2 of the 5 instances adhesions in the deperitonealized pelvis resulted in obstruction necessitating laparotomy.

POSTERIOR PELVIC EXENTERATION

This term is applied to the operations consisting of en masse excision of pelvic colon, uterus, vagina, and adnexae, with or without pelvic node excision. It is carried out usually for carcinoma of the rectum extending forward to involve the gynecologic tract, but is also indicated for cancer of the gynecologic tract that may extend backward to involve the rectum. It is not a new procedure although in most instances a really complete removal of vagina, uterus, and adnexae with rectal colon was not performed. It represents essentially an extended classical abdominoperineal resection of the rectosigmoid, and therefore this group of patients is not considered in this report. The fact that the lower urinary tract is undisturbed renders the operation simpler and less hazardous than anterior pelvic exenteration and, of course, much less involved than total pelvic exenteration.

DISCUSSION

As palliation was the only objective envisaged when the operations described were

introduced, this still remains an important objective of the procedures. Just how to evaluate and interpret palliation is difficult to define. Certainly survival for 3 years without evidence of disease after disease was present to such an extent that an exenteration procedure was carried out represents palliation. This result was achieved in 28 per cent of 89 patients operated upon in the period from 1950 to 1951. The authors, however, believe that even several months' respite from the symptoms presenting before operation also constitutes palliation, and this was achieved in a higher incidence than the statistics given indicate.

That patients could survive "5 years" free from disease was a situation not considered possible when exenterations were first systematically carried out. Experience, however, has shown that this is possible, and hence these operations do afford "cures" from advanced pelvic cancer that has spread to involve two or all the major pelvic viscera. The 5 year cure rate is found to be 12 per cent among 104 patients, which is a greater salvage than is possible for *advanced* cancer of the lung, stomach, pancreas, esophagus, or gallbladder, achievable by surgery.

It would appear, therefore, that the exenteration operations are not futile procedures but are capable of affording effective palliation and "cure." Therefore, the discussions concerning their propriety are no longer in order. The questions in order are: Does the surgeon wish to undertake them? If so, does he possess the necessary background and does he have sufficient personnel and facilities available to him in order to assure maximal opportunity for survival of the patient and proper after care? The proper after care for patients that receive total pelvic exenteration is more involved than with any other type of surgical operation.

In the presence of advanced pelvic cancer uncontrolled by radiation (if it is of gynecologic origin), the physician should have full cognizance of the possibilities of the exenteration operations and be fully aware of his responsibility to the patient and family before he states more or less empirically that "nothing further can be done." Something further can be offered these patients if disease is limited to the pelvis but the situation must be fully explained to them. It is the practice of the writers to take the family into confidence and explain the diagnosis, the extent of the operation, the risks inherent in the procedure, the fact of permanent physiologic and anatomic alterations as a result of the operations and the chances for palliation and "cure"; also the alternatives if nothing is done. One thing is certain, these patients, if nothing is done, do not "die in peace." With the family's approbation the patient is next interviewed. The word "cancer" is not and need not be mentioned. The patients usually realize what they have, and there is no necessity to dramatize and emphasize their desperate straits by overt mention of "advanced cancer." The surgeon must never frighten a patient into an affirmative decision to have the operation. The altered physiologic and anatomic status resulting from the operation is explained to the patient. Often a patient who has survived the procedure for 3 to 6 years is requested to talk with the prospective patient and to demonstrate adjustment to the wet colostomy and return to full physical activity. In only rare instances have patients refused the operation when it has been proposed. It is our contention that it is beyond the province of any one physician to be the sole judge of whether or not a patient may

TABLE V.—"FIVE YEAR" RESULTS IN EXENTERATION OPERATIONS (4 TO 6½ YR. SURVIVORS)

No. of patients	Year of operation	Living and well	Per cent survival
13	1947	3	23
49	1948	4	8
42	1949	5	12
Total 104	1947–1949	12	12

TABLE VI.—TWO TO 4 YEAR RESULTS IN EXENTERATION OPERATIONS

No. of patients	Year of operation	Living and well	Per cent survival
38	1950	9	24
51	1951	18	35
Total 89	1950–1951	27	30

have one more chance for palliation without giving her an opportunity to gamble for chances for benefit and even cure. In such situations as these, the patient and the family must take part in the final decision with full realization of the dangers and disappointments that may follow the operation. Exenteration operations must not be urged in the manner that appendectomy is insisted upon in acute appendicitis; neither is it in order for one physician to state that the patient were better off dead than to live after a total exenteration with its permanent alterations in anatomic and physiologic status of the pelvis.

There are compensations to continued existence free from pain, with adjustment to the wet colostomy, and return to more or less full physical activities, which, actual experience has shown, outweigh the disadvantages of alterations in the pelvis incident to total exenterations.

When, as in most instances, the operation does not result in the desired palliation or 5 year survival, it is easy for some to criticize the attempt and to pronounce its original futility. Actual experience, however, in a significant series of patients would belie such criticism. Unfortunately, the present state of knowledge is such that this type of surgery has to be done in order to give the patient one last chance for relief. The fact that the majority of attempts fail is no reason to refuse all patients their one remaining opportunity for benefit. They and their families, as stated before, should be made cognizant of these opportunities and at the same time be made aware of the fact that the chances for desired results are less than the probabilities of failure, but that there is much more than a slight chance for appreciable relief cannot be denied. The patients reported herein represent an initial series in this type of surgery. Such exploratory endeavors always include operations that should not have been done. If these were excluded and other devices employed to enhance the apparent incidence of successes artificially, the results here reported would compare not unfavorably with the results of less radical procedures for so-called operable carcinomas in some other viscera.

SUMMARY

1. Total pelvic exenteration and anterior partial pelvic exenteration for advanced pelvic cancer are operations which can afford effective palliation and also 5 year "cures" when no other known method of treatment can afford opportunity for comparable relief.

2. Statistics concerning surgical mortality in 315 minimally selected patients and concerning palliation and 5 year survival rates are presented.

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CORRELATION OF LIVER BIOPSY FINDINGS WITH SURGICAL DISORDERS OF THE UPPER PART OF THE ABDOMEN

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BIOPSY of the liver has in the past few years assumed a major role in the diagnosis of hepatic disease. Perfection of the technique of needle biopsy has contributed much toward this advance and has stimulated an increased interest in the evaluation of hepatic structure and microscopic pathologic changes. Much work has also been done in attempting to correlate microscopic structure and hepatic function, as summarized by Popper. From these standpoints, the appearance of the liver in various diseases has been clarified considerably.

Although the healthy liver has been studied by Elias (5, 6) in respect to microscopic anatomy, and the anatomic changes have been correlated with physiologic alterations by Knisely, we believe that not enough attention has been paid to the ranges of variability microscopically exhibited by what we usually think of as the "normal" liver. The work of Mateer and co-workers, who took biopsy specimens at operation on a number of patients with cholecystitis and with peptic ulcer, was pioneering in this regard in that it showed a surprising number with hepatic abnormalities. However, these authors used the appearance of the liver of a healthy child as their criterion of normality.

It was the intention of our study to evaluate in a series of surgical biopsies of the liver: (1) the effect of various upper abdominal conditions on the appearance of the liver, (2) the average picture found in a series of patients with grossly appearing relatively normal livers, and (3) any variations in microscopic picture that makes surgical biopsy specimens differ from specimens taken by other means.

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Abridgment of thesis submitted by Dr. Dunlap to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

BACKGROUND INFORMATION

Several authors have noted what they consider to be characteristic changes in the appearance of the liver in various upper abdominal conditions. Ireneus, in acute pancreatitis experimentally produced in dogs, noted varying degrees of atrophy and edema in central and periportal areas. The central sinuses were dilated with cells and debris, the cell outlines were not clear, fatty changes were sometimes seen, and in severe cases necrosis and hemorrhage occurred. Knight and co-workers found a high incidence of hepatic cirrhosis concomitant with pancreatitis. Many livers also exhibited pericholangitis. Two of 7 livers studied showed retention of bile and 2 showed fatty infiltration.

Carajannopoulos found, in 23 patients with peptic ulcer, increased portal infiltration, albuminoid, vacuolar, or fatty degeneration of hepatic cells, and polymorphonuclear infiltration of the hepatic lobules.

A change described by Anderson and Warren and chiefly associated with diabetes mellitus is that of vacuolation of the nuclei of hepatic cells due to depletion of cytoplasmic glycogen within the nucleus. They observed that it apparently is more common in patients with uncontrolled diabetes but is also present in about 20 per cent of nondiabetics. Cell nuclei appear clear centrally with the chromatin either crowded to the periphery or absent entirely.

It was obvious from the report of Mateer and co-workers that the average picture seen in patients with relatively normal livers was not like that seen in a healthy child. Only 6 per cent of 163 patients studied showed this

TABLE I.—OPERATIVE DIAGNOSIS IN 88 CASES IN WHICH BIOPSY SPECIMENS WERE REMOVED FROM THE LIVER AT OPERATION

Surgical diagnosis		No. of cases
Cholecystitis		15
Alone	14	
With intestinal obstruction	1	
Pancreatitis		18
Alone or with pseudocyst formation	5	
With cholecystitis	10	
With common duct obstruction	3	
Common duct obstruction alone		7
Peptic ulcer		38
Alone (duodenal, gastric, recurrent)	33	
With cholecystitis	2	
With common duct stone	1	
Carcinoma of stomach	1	
Indeterminate gastrointestinal bleeding	1	
Others		10
Carcinoma of pancreas	3	
Indeterminate abdominal pain	3	
Carcinoma of colon	2	
Splenomegaly	1	
Lipomas and diverticula of colon	1	
Total		88

degree of normality. In slightly less than half of all their cases there was a slight increase in fibrous tissue and lymphocytic infiltration. In another large group, roughly a third of their cases, there was a rather decided increase in fibrous tissue and portal infiltration with mononuclear cells.

There are many reasons to make one believe that the microscopic appearance of surgical biopsy specimens of hepatic tissue might be different from that of specimens taken by other methods. That function of the liver is impaired in most patients following an operation or anesthesia alone has been shown by many observers, including Boyce, Schmidt, and Tagnon and their co-workers. The etiologic factors in the production of this temporary change have not been generally agreed upon but are thought to be either the toxicity of the anesthetic agent or anoxia, according to Ravdin and Vars, and Tagnon and co-workers.

Keller and Smetana have described what they believe to be artefacts peculiar to surgical biopsy specimens of the liver produced at the time of operation by trauma to the lobes of the liver. They speak of (1) focal accumulations of polymorphonuclear leucocytes in areas of focal necrosis of the hepatic cells, (2) subcapsular infiltration of neutrophils, and (3) subcapsular or parenchymal hemorrhages. The same polymorphonuclear leucocytic infiltration was said by Mateer and co-workers to occur in 10 to 15 per cent of their cases, except that it was not observed in areas of focal necrosis. These workers considered this to represent a reaction related either to a nearby inflammatory process or to a generalized disease, as evidenced by an increased leucocytic count in the peripheral blood.

In any discussion of biopsy of the liver, reference should be made to the multiple biopsy study of Waldstein and Szanto. Their investigations led them to the conclusion that although injury of hepatic cells and fatty changes were fairly uniform in distribution throughout the liver, alterations in lobular pattern, scarring, periportal inflammation, and over-all leucocytic reaction, with or without focal necrosis, were subject to great distributional variations and could not be determined with certainty on the basis of 1 biopsy specimen alone.

TABLE II.—DISTRIBUTION OF CASES ACCORDING TO SURGICAL DIAGNOSIS AND THE OCCURRENCE OF FATTY METAMORPHOSIS

Surgical diagnosis	No. of cases		
	Total	Increased fat	
		No.	Per cent
Cholecystitis	15	3	20
Pancreatitis	18	1	6
Common duct obstruction	7	1	14
Peptic ulcer	38	3	8
Others	10	2	20
Total	88	10	11

MATERIAL AND METHOD

Wedge biopsy specimens were removed from the liver of 88 patients undergoing operations for upper abdominal conditions. In 38 of these cases 2 specimens were removed, 1 at the beginning and 1 at the end of operation, in order to show the changes which took place during the interval. This forms the basis for another report by us (4) and will be referred to only briefly in this article. Each specimen was placed in 10 per cent formalin for 24 hours and then fixed frozen sections were made and

stained with hematoxylin and eosin. Occasionally, special stains using paraffin blocks were employed. Excluded from the study were all cases in which there was primary or marked secondary disease of the liver except for several cases in which mild obstructive jaundice was present. The diagnoses in the cases included in this study are presented in Table I. General groupings have been made for the purpose of correlation.

All sections were studied as unknowns. An attempt was made to evaluate and to classify all the microscopic features seen and to grade degrees of each change seen. From the study of this group of normal biopsy specimens there emerged six categories of pathologic change. These were: (1) fatty metamorphosis, (2) fibrosis, (3) portal inflammatory reaction, (4) nuclear regenerative and degenerative activity, (5) nuclear vacuolation, and (6) parenchymal polymorphonuclear leucocytic infiltration.

At operation various factors were noted, such as appearance of the organs, type and duration of anesthesia, blood pressure variations, and types of fluids used intravenously. Records were reviewed in each case in order to note age, sex, duration, and character of their illness, and x-ray and laboratory studies performed preoperatively.

RESULTS

General microscopic features (Figs. 1 and 2). Fat.—In only 10 of the 88 cases did the biopsy specimens demonstrate an increased amount of fatty change, that is, more than a few droplets of fat in any field (Fig. 1b). The distribution of these cases according to clinical group (surgical diagnosis) is shown in Table II.

The figures are small and do not vary significantly. It is interesting to note the virtual absence of fat in the cases of pancreatitis, in view of the usual association of this condition with alcoholism. We were unable to determine from the records the exact extent of the alcoholism, but among 6 known alcoholics in the entire series, only 1 showed significant fatty change, and this patient did not have pancreatitis. This probably reflects the general good state of nutrition in the group studied. When the 38 biopsy specimens taken at the beginning of operation were compared with those taken after operation, there was no evidence of change in the amount of fat present.

TABLE III.—DISTRIBUTION OF CASES ACCORDING TO SURGICAL DIAGNOSIS AND THE OCCURRENCE OF INCREASED FIBROSIS

Surgical diagnosis	No. of cases		
	Total	Increased fat	
		No.	Per cent
Cholecystitis	15	7	47
Pancreatitis	18	7	39
Common duct obstruction	7	4	57
Peptic ulcer	38	24	63
Others	10	7	70
Total	88	49	56

Fibrosis.—Normally, the fibrous tissue present in the lobule of the liver is found in the portal triad and around the larger vessels. Abnormal bands of scar tissue were not demonstrated in our cases, so that evaluation was made chiefly on the basis of the amount of fibrous tissue present in the portal spaces (Fig. 1c). It has been demonstrated that there is great variation in the amount present in different lobules; however, an average of the general picture in each slide was found to be fairly accurate. In our group of 38 cases in which 2 biopsy specimens each were taken, there were practically no differences between the amount of fibrous tissue found at the

TABLE IV.—DISTRIBUTION OF CASES ACCORDING TO SURGICAL DIAGNOSIS AND INCREASE OF PORTAL INFLAMMATORY INFILTRATION

Surgical diagnosis	No. of cases		
	Total	Portal infiltration	
		No.	Per cent
Cholecystitis	15	8	53
Pancreatitis	18	11	61
Common duct obstruction	7	6	86
Peptic ulcer	38	17	45
Others	10	5	50
Total	88	47	53

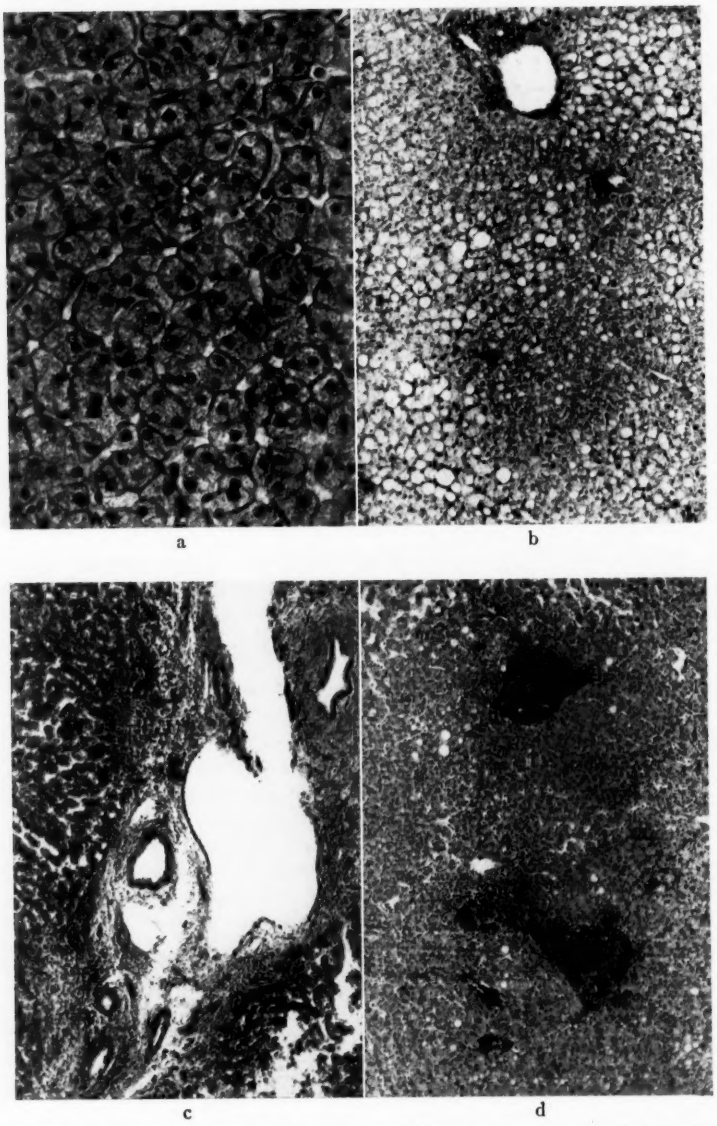
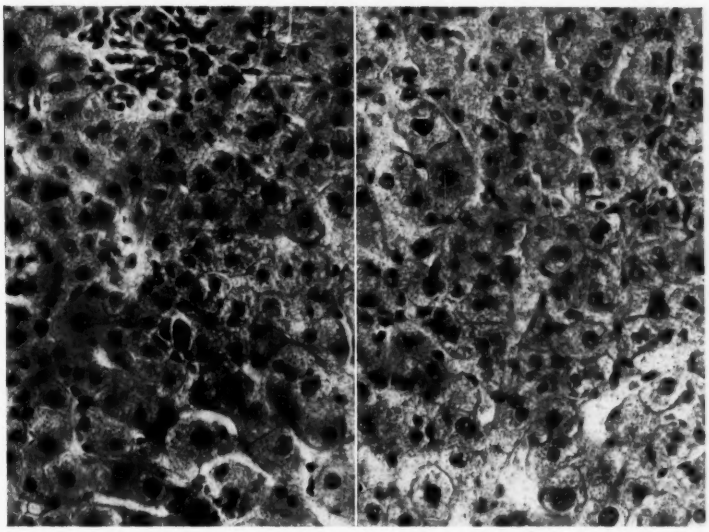


Fig. 1. a, Minimal alteration of hepatic parenchyma as seen in a so-called normal control. Only an occasional doubly nucleated cell is seen and nuclear crenation is practically absent. Hematoxylin and eosin, ×278. b, Grade 3 fatty metamorphosis is exhibited by this otherwise normal liver. Hematoxylin and eosin, ×59. c, Grade 3 periportal fibrosis, still apparently within the so-called normal range. Hematoxylin and eosin, ×59. d, Fairly marked (grade 3) periportal inflammatory infiltration with minimal fatty change in an apparently normal liver. Hematoxylin and eosin, ×59.



a b

Fig. 2. a, The normal phenomenon of regeneration of hepatic cells is apparently accelerated here. Note the variation in nuclear size, the presence of doubly nucleated forms, and the prominence of nucleoli. Hematoxylin and eosin, ×278. b, In this section taken from the same block as, a, there are accelerated degenerative phenomena. The cellular outlines are not clearly delineated and many of the nuclei are crenated and pyknotic. Hematoxylin and eosin, ×278.

beginning of operation and that found after operation.

Forty-nine of the 88 livers studied were believed to show an increased amount of fibrous tissue in comparison with 39 others which were considered normal. The distribution by clinical group is shown in Table III.

It is perhaps significant that the patients with cholecystitis and pancreatitis showed considerably less fibrosis than did those with peptic ulcer. This fact may be explained in part on the basis of the relation of fibrosis to the age of the patient and the duration of his symptoms prior to operation. The average age in 39 patients with normal livers was 49.7 years and in 49 patients with increased fibrosis was 51.9 years. The average duration of symptoms in these same cases was 5.8 and 7.4 years respectively. Fibrosis was increased slightly with increase of age and duration of symptoms. In general, the patients with peptic ulcer were older and gave a history of difficulty of longer-standing than did those with cholecystitis, as shown later in the paper.

There is good correlation of duration of symptoms with presence of increased fibrosis. The age factor may be better demonstrated by dividing the group at 60 years. Half of the patients who were less than 60 years of age showed increased fibrosis, whereas two-thirds of those who were 60 years of age or over demonstrated this change.

Portal inflammation.—Inflammatory round-cell infiltration in the portal triad, "pericholangitis" or "triaditis" as it is sometimes called, was also somewhat irregular in its distribution as regards the various portal spaces seen in 1 biopsy section alone. However, if one or more spaces were filled or bulging with cellular infiltrate, the section was considered to have an increased amount over the normal and was so categorized (Fig. 1d). Forty-seven of the 88 patients showed an increase in the amount of portal cellular infiltrate as compared to the other 41 who demonstrated minimal infiltration (Table IV).

Portal inflammation was present in all but 1 of the cases of common duct obstruction, and

TABLE V.—DISTRIBUTION OF CASES ACCORDING TO SURGICAL DIAGNOSIS AND THE OCCURRENCE OF INCREASED NUCLEAR REGENERATION AND DEGENERATION

Surgical diagnosis	No. of cases				
	Total	Increased regeneration		Increased degeneration	
		No.	Per cent	No.	Per cent
Cholecystitis	15	10	67	11	73
Pancreatitis	18	8	44	11	61
Common duct obstruction	7	3	43	3	43
Peptic ulcer	38	23	61	18	47
Others	10	6	60	7	70
Total	88	50	57	50	57

in this case symptoms were of very brief duration. The biopsy specimen was also quite small in this case and showed only a few portal spaces. In each of the other conditions the proportion of patients who had portal inflammation showed no great variation from the average for the entire series.

Of 6 diabetics, 4 showed an increase in portal infiltration. In the group of 38 patients who underwent biopsy there were 4 additional patients who had portal inflammation at the end of the operation but who did not have it at the beginning of the operation. No correlation could be made between the degree of fibrosis and the amount of portal infiltration present.

Evidences of nuclear regenerative and degenerative activity.—The processes of regeneration and degeneration are occurring constantly in any normal liver. Since in our group of patients there were not such marked variations as the cellular necrosis of hepatitis or the nodular regeneration of cirrhosis, evaluation was made on the basis of nuclear variations. Regeneration is shown by the presence of double nuclei, large nuclei, multiple nucleoli, marked staining variations, or variation in nuclear size in a given portion of the lobule (Fig. 2a). Degenerating nuclei show mild to marked crenation and sometimes pyknosis (Fig. 2b). It was possible to separate a group of 50 cases in which there was quite definite regeneration and another group of 50 in which there was quite definite degeneration, as compared with 38 normals in each instance (Table V).

Both regeneration and degeneration appeared to occur in cholecystitis in a higher percentage of cases than they did in the other conditions. A check of these figures was made by adding to them all the cases of cholecystitis included in the major categories of pancreatitis and peptic ulcer. This addition did not alter the percentages. There were fewer patients with increased nuclear regeneration and degeneration in the group with obstruction of the common duct, but the numbers were small and this could not be considered significant.

When the biopsy specimens taken at the beginning of operation were compared with those taken at the close of operation in the 38 cases in which this procedure was followed, an increase in the number showing definite regeneration and degeneration was noted: 3 of the former and 6 of the latter type of change. The significance of this observation is probably only that in some few cases there was an increase, whereas in none was there a decrease in activity during operation.

TABLE VI.—DISTRIBUTION OF NONDIABETIC CASES ACCORDING TO SURGICAL DIAGNOSIS AND THE OCCURRENCE OF VACUOLATION OF NUCLEI

Surgical diagnosis	No. of cases		
	Total	Vacuolation of nuclei	
		No.	Per cent
Cholecystitis	13	4	31
Pancreatitis	16	3	19
Common duct obstruction	7	0	0
Peptic ulcer	37	6	16
Others	9	4	44
Total	82	17	21

Vacuolation of nuclei.—In 21 of the 88 cases the phenomenon described by Warren and by Anderson as vacuolation of nuclei was seen in some areas of the sections. Groups of cells with vacuolated nuclei were present in clusters, usually in the peripheral portions of the lobules, as noted by Warren. Many nuclei appeared completely empty; in others the chromatin was crowded to the periphery of the nucleus leaving the center clear.

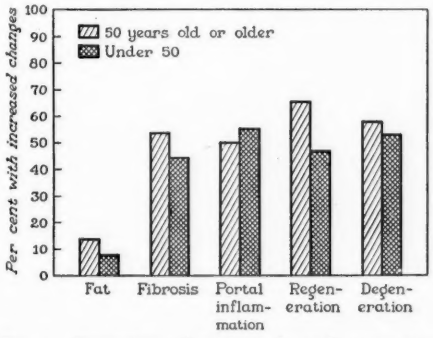


Fig. 3. Percentage of patients in each age category whose biopsy specimens showed increased changes.

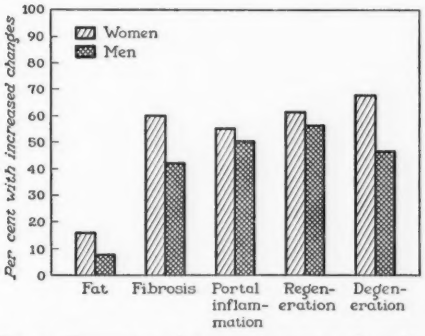


Fig. 4. Percentage of men and women whose biopsy specimens showed increased changes.

This change is recorded as being more prominent in diabetics. In our group it was present in 4 of the 6 diabetics. It is of interest that in both cases in which vacuolation was not present the patients had chronic pancreatitis, but the significance of this is not known, since among the nondiabetics the incidence of this phenomenon in cases of pancreatitis was essentially the same as the average for the entire group of nondiabetics (Table VI). Vacuolation was not seen in nondiabetics when obstruction of the common duct was present. The average for the group (21 per cent) is consistent with the 20 per cent cited by Anderson as the incidence of nuclear vacuolation among the nondiabetic population. Unfortunately we were unable to obtain glycogen stains of any significance, since our specimens had all been preserved in formalin at the time they were studied.

TABLE VII.—DISTRIBUTION OF PATIENTS ACCORDING TO SURGICAL DIAGNOSIS AND AGE

Surgical diagnosis	No. of cases		
	Total	Age, years	
		Less than 50	50 or more
Cholecystitis	15	7	8
Pancreatitis	18	10	8
Common duct obstruction	7	3	4
Peptic ulcer	38	15	23
Others	10	3	7
Total	88	38	50

Polymorphonuclear leucocytic infiltration.—Infiltration of the parenchyma and sinusoids near central veins by clusters of polymorphonuclear leucocytes was a phenomenon found to occur during the course of the operation, as shown in the 38 cases in which biopsy specimens were taken at the beginning and at the end of the operation. Only 11 per cent of the initial biopsy specimens showed any such infiltration, whereas 34 per cent of those taken at the close of operation showed marked infiltration and an additional 40 per cent demonstrated minimal change. This forms the subject of another communication to be published separately (4). It was concluded that the basis of this phenomenon was probably a traumatic artefact caused by retractors and manipulation.

Correlation of certain clinical features. Thirty-eight of the patients were less than 50 years of

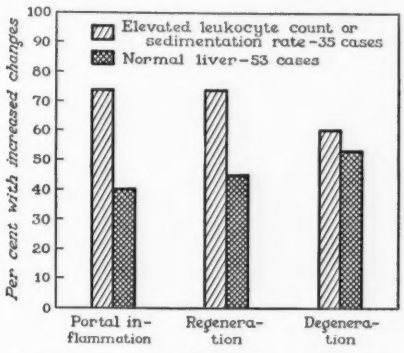


Fig. 5. Presence of inflammatory disease.

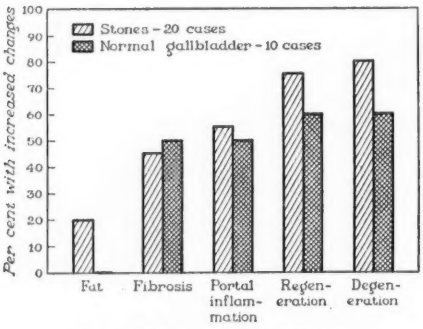


Fig. 6. Disease of the gallbladder.

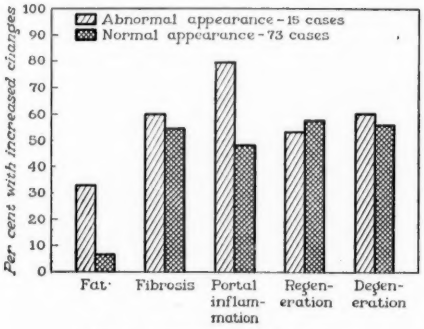


Fig. 8. Appearance of the liver.

age and 50 were 50 years old or older (Table VII). Figure 3 shows that all the microscopic features except portal inflammation were slightly more pronounced in the older age group. This is particularly true in the case of regenerative activity.

Fifty patients were men and 38 were women (Table VIII). An obvious weighing of the statistics occurred since peptic ulcer belongs largely to the men and gallbladder disease to the women. Figure 4 shows that there was a consistently greater number of women than men showing an increase in the described microscopic features.

The presence of inflammation in the body, as indicated by an elevated leucocyte count or sedimentation rate, was shown in 35 of the 88 cases in this series. When these were compared with the 53 normals, the results seen in Figure 5 were obtained. It is evident that portal inflammation was more common when generalized inflammation was present than when it was not. This was also true of regeneration of nuclei but not to any great degree of degenerative change. Fatty change and fibrosis showed no variations when the groups were compared.

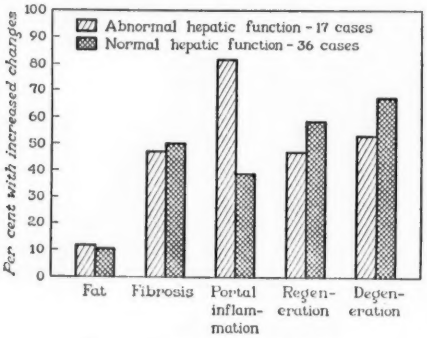


Fig. 7. Liver function studies.

Among our 88 patients, 10 had roentgenograms of the gallbladder that were reported as disclosing no abnormality. In 20 other cases the presence of stones and chronic cholecystitis was disclosed either on x-ray examination or at operation. There were no cases of acute cholecystitis in this series. Figure 6 shows that in regard to each feature, with the exception of fibrosis, increased changes were more common in the group of patients showing evidence of gallbladder disease than in the group with a normal gallbladder. These two groups varied least with respect to portal inflammation and fibrosis.

In 17 of our cases the results of one or more liver function tests were abnormal, while in 36 other cases the results were normal (Fig. 7). The illustration shows that portal inflammation was more prevalent in the former group than in the latter. This increased prevalence in the former group is weighed by the inclusion of patients with mild obstructive jaundice. It is interesting that increased regenerative and degenerative activity was more common in the normal group than in the abnormal group.

In 15 cases in our series mention was made in the operative notes that the liver appeared to be "rounded," "firm," "enlarged," "fatty," "congested," or the site of "hepatitis." When

TABLE VIII.—DISTRIBUTION OF PATIENTS ACCORDING TO SURGICAL DIAGNOSIS AND SEX

Surgical diagnosis	Total	Male	Female
Cholecystitis	15	3	12
Pancreatitis	18	10	8
Common duct obstruction	7	3	4
Peptic ulcer	38	29	9
Others	10	5	5
Total	88	50	38

these cases were compared with the 73 cases in which the livers were considered normal by the surgeon, two features stood out prominently—both fatty change and portal inflammation appeared to contribute most to the abnormal appearance of the liver (Fig. 8).

COMMENT

The foregoing results are tabulated not so much for their pathologic or surgical significance as for a base line in showing the variations in microscopic appearance that may occur in livers which are generally considered normal. The liver of a healthy child, as used by Mateer and co-workers represents too strict a criterion for practical use to distinguish the normal from the abnormal liver. In our series the one group less likely to come into the normal class consisted of the patients with mild obstructive jaundice. Patients so affected showed the highest percentage of portal inflammation and other abnormal appearances of the liver.

In general our results agree remarkably well with those of Mateer and co-workers, particularly when the numbers showing increased fibrosis and portal inflammatory reaction are compared. When our figures are combined, they are very similar to theirs. We have also noted with interest that our findings in regard to normal surgical biopsy specimens were very much like the changes described by Carajannopoulos in biopsy specimens from patients with peptic ulcer. It is possible that had he run a series of controls in other upper abdominal conditions, he might have found changes similar to those he described as characteristic of peptic ulcer. In general, we have found few if any distinguishing features in surgical biopsy specimens of the liver which are characteristic of any particular upper abdominal condition. This excludes the obvious exception of obstruction of the common duct. A much larger series than this would be necessary if statistically significant results are to be obtained.

SUMMARY

In the study of a series of 88 patients with normal or nearly normal livers who underwent biopsy of the liver at the time of operation, the following observations were made:

1. Increased fatty metamorphosis was present in 11 per cent of the patients.

2. An increase in the amount of fibrosis, portal space infiltration, and nuclear regenerative and degenerative activity was noted in approximately half of the cases.

3. The microscopic changes did not appear to be significantly related to the type of surgical disorder present except in the cases of obstruction of the common duct, in which a high percentage of specimens exhibited portal inflammation.

4. Fibrosis increased with age and with increased duration of symptoms of the disease.

5. Vacuolation of nuclei was present in two-thirds of the diabetics and in about a fifth of the nondiabetics.

6. Changes were more prevalent in the biopsy specimens from older persons and in those from women.

Correlation of other clinical features with microscopic appearance is shown in graphs.

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THE INFLUENCE OF ANTIBIOTICS ON EXPERIMENTAL ENDOGENOUS PERITONITIS

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INFECTIONS of the peritoneum still present a problem of great magnitude in general surgery. The large number of papers published each year on this subject is indicative of the widespread interest in the problem. Despite much research, our knowledge of many facets of this disease is still incomplete. The reduction recently evident in the annual mortality rate of peritonitis represents the summation effect of improved prophylaxis, earlier diagnosis, better management, antibiotic therapy, and the correction of perverted metabolic, protein, electrolyte, and water balance.

It is exceedingly difficult to evaluate by mathematical formulas the relative significance of any one of these therapeutic measures in man. During the phenomenal development of new antibiotics in the past 12 years, some confusion has resulted regarding the comparative value of these various agents in the clinical management of acute bacterial peritonitis. Although surgeons agree that chemotherapy is of great value, there is little agreement as to the best agent to use or the best manner of its application. Even less is known regarding the influence of antibiotics on the local and systemic effects of the disease. For these reasons, the studies to be reported in this article were undertaken. The first objective was to evolve a technique for the uniform production of lethal, diffuse, acute peritonitis in laboratory animals. The second consideration was the role certain antibiotics play in influencing the host responses to this disease process.

EXPERIMENTAL METHOD

Certain conditions are necessary for the induction of lethal experimental peritonitis. They include (1) the presence of materials in the peritoneal cavity, such as devitalized tissues, feces, blood, bile, gastroduodenal contents, or foreign bodies, together with (2) bacteria in sufficient numbers, varieties, and virulence to produce infection, and (3) a host susceptible to the stress produced by this combination of factors. The production of lethal peritonitis in dogs is usually accomplished by ligature necrosis of the appendiceal appendage which has been manually distended with colon contents, together with the removal of the omentum at the time of celiotomy, followed by stimulation of bowel motility by oral administration of 2 or 3 ounces of castor oil (Bower's technique). This method has the double disadvantage of robbing the body defense mechanisms of the omentum, which plays an important role in aiding the localizing process of the infection, and of producing hypermotility of the intestine.

The use of dogs limits the number of experiments which can be performed because of the demand upon operating and maintenance facilities as well as cost and time.

We, therefore, sought to produce in a smaller animal a lethal diffuse endogenous peritonitis which would be easily and readily reproducible. The purpose was to use the method to screen the efficacy of various antibiotic therapeutic regimens in a sufficient number of animals to permit statistical evaluation of the data. With the technique to be described—perforation of the cecum followed by the introduction of mucin into the peritoneal cavity—1 operator and 1 assistant were able to induce peritonitis in as many as 30 animals in a single day.

The rat was chosen as the experimental animal, with the knowledge that its fecal flora, while qualitatively the same as that of

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the dog and of man, differs in the proportions of several of the species in the mixture. Specifically, clostridia and micrococci are present in fewer numbers in the rat. It was believed that any discrepancies resulting therefrom could be resolved by subsequently testing in dogs those antibiotics which had given the best survival rates in rats. Essentially the same technique which was employed in rats induced acute, diffuse, lethal peritonitis in dogs.

Details of the experimental method. Adult white rats, varying in weight from 120 to 180 grams, were used. Anesthesia was induced with sodium pentobarbital, 40 milligrams per kilogram of body weight, administered intraperitoneally. After preparation of the surgical field, the peritoneal cavity was entered through a low right paramedian incision. The cecal pouch was delivered into the wound, a 3 to 4 millimeter incision was made in the pouch, and the lips of the wound were cauterized with a heated iron wire to produce necrosis and to keep the wound open. A small amount of feces was then expressed into the peritoneal cavity, and the perforated cecum allowed to drop back into the peritoneal cavity. The abdominal wall was closed en masse by suture and the wound was overlaid with collodion solution.

This procedure resulted in a mortality of only 5 per cent of the animals. At autopsy the cecal fistula was surrounded by a varying degree of inflammation and was usually closed by a plug of omentum.

It was then decided to test the intraperitoneal injection of sterile mucin for the purpose of retaining the bacteria in the peritoneal cavity long enough to establish a peritonitis which would prove fatal. Our in vitro studies indicated that mucin did not interfere with the antibacterial action of penicillin and streptomycin. We found that the injection of mucin, one component of which, according to Smith and associates, is heparin, into normal rats did not result in any aberrations in blood clotting time. The exact role of mucin in enhancing infections has not been fully determined. It has been postulated that infection is aggravated by virtue of the viscosity and particulate residue of the material, which combine to retain the micro-organisms in the peritoneal cavity, while at the same time the mucin temporarily retards phagocytosis. In any event, bacteria are enabled to survive so that a focus of active infection is established in the peritoneal cavity.

The mucin suspension was prepared by emulsifying 100 grams of hog gastric mucin in a liter of distilled pyrogen-free water and autoclaving for 15 minutes at a 15 pound pressure. The *p*H was adjusted to 7.3 with sodium hydroxide. While the rat was still under anesthesia, 2 milliliters of the sterile suspension were injected into the peritoneal cavity.

The remarkable effectiveness of mucin in enhancing bacterial invasion is readily apparent from a simple comparison. The animals receiving no mucin showed only minimal peritoneal reaction and a mortality rate of 5 per cent, while rats injected with the mucin suspension postoperatively consistently developed an intense peritoneal infection. Of 664 animals used as untreated controls, only 14 per cent survived, a mortality rate of 86 per cent. Untreated animals became acutely ill, lethargic, and humped up, and their fur appeared ruffled. The abdominal cavity became progressively distended and their condition deteriorated rapidly until death. The average survival period was 22.7 hours. In contrast, animals likely to recover reacted within 18 hours after operation by (1) becoming more alert and active, (2) having smooth and glossy fur, (3) showing curiosity and responsiveness to stimuli, (4) resuming eating and drinking habits, and (5) showing a regression of abdominal distention.

Examination of the peritoneal cavity of rats dying from peritonitis revealed 4 to 8 milliliters of viscous, odoriferous fluid of *p*H 7.8 to 8.0. There was a diffuse inflammatory process throughout the peritoneum, with marked engorgement of the blood vessels. The abdominal viscera had lost their normal glistening appearance. Intestinal fistulas had remained patent. Varying amounts of fibrinous exudate were deposited about the peritoneal cavity. No visceral pathologic changes were noted and peritoneal abscess was conspicuously absent. Smears of the peritoneal

exudate showed numerous leucocytes, many of which were fragmented. Numerous bacteria were seen, of which the great majority were extracellular.

In animals which recovered, the peritoneal exudate was usually diminished in amount, cellular content, and bacteria. These animals nearly always showed omental plugging or, less commonly, sealing of the perforation by matting of the intestines. These findings are in definite contrast to those in animals which died from peritonitis.

Sampling experiments indicated that infection was present within 4 hours after operation. This, therefore, was the interval chosen for institution of antibiotic therapy with antibiotics obtained on the open market. The routes of administration were (1) oral, (2) intramuscular, (3) intravenous, (4) intraperitoneal, (5) intramuscular-intraperitoneal, (6) intravenous-intraperitoneal, or (7) oral-intraperitoneal.

After pilot experimentation with a wide range of doses, a single dose of 40 milligrams per kilogram of antibiotic (about 5 mgm.), dissolved in 0.25 cubic centimeter of pyrogen-free distilled water, was selected for treatment. Chloramphenicol was given in a solution of acetyldimethylamine, as supplied by the manufacturer. Control animals received 0.25 milliliter of 0.9 per cent sterile saline. After treatment, the animals were returned to their cages, where adequate water and food were readily available. No attempt was made to maintain adequate water and electrolyte intake by infusion.

All control and antibiotic-treated animals which died within 8 hours postoperatively were eliminated from the series. These early deaths were attributed to a combination of operative shock, dehydration, and overwhelming sepsis. Animals which survived for 72 hours or more were considered survivors. They were sacrificed and the autopsy findings were recorded. Aerobic and anaerobic bacteriologic cultural studies were conducted routinely on the peritoneal exudate, and, in some instances, on the heart blood.

In the hematologic studies, rats were anesthetized with ether, and blood was obtained from the jugular vein. Leucocyte counts were made with the usual pipettes and diluting fluid; differential counts were made on smears stained with Wright's stain. Antibiotic levels in peritoneal fluid and in the blood plasma were assayed by the serial tube dilution technique.

Essentially the same technique which was used in rats was also used to induce an acute, diffuse, lethal peritonitis in dogs. Adult male mongrel dogs which had previously been immunized against rabies and distemper were used. Their weight ranged between 9 and 14 kilograms. Anesthesia was induced by the intravenous injection of sodium pentobarbital in a dosage of 26 milligrams per kilogram of body weight. After preparation and draping of the operative field, the peritoneal cavity was entered through a low midline incision and the cecum was delivered into the wound. A 5 to 7 millimeter incision was made in the cecal pouch and the lips of the wound were cauterized in the same manner as in the rat. A small amount of cecal contents was expressed into the peritoneal cavity. The celiotomy wound was then repaired by suture in layers. Following closure, 10 per cent gastric mucin (2.2 ml. per kgm. of body weight) was injected intraperitoneally. In the first experiments, a rubber tube drain was brought out of the peritoneal cavity through a stab wound in the left lower quadrant for the purpose of obtaining samples of peritoneal exudate. Plugging was frequent, and this procedure was later abandoned in favor of intraperitoneal punctures, for which a 19 gauge needle and syringe were used. In untreated animals, the average survival time was 22.6 hours.

Sampling experiments indicated that infection was present 2 hours after operation and this time was chosen for administration of the antibiotics to be tested. As in the rat, a single dose of 40 milligrams per kilogram of body weight was given. The routes of administration were the intravenous and the combined intravenous and intraperitoneal. The antibiotics tested were oxytetracycline, tetracycline, and a combination of 20 milligrams per kilogram each of penicillin and streptomycin. Blood, urine, and peritoneal exudate were drawn at intervals and the spec-

imens analyzed for antibiotic concentrations. Leucocyte counts were made on the blood samples. The peritoneal fluid was also subjected to aerobic and anaerobic bacteriologic analyses and total bacterial counts.

RESULTS IN RATS

The results with the various routes of administration of antibiotics in the rat peritonitis preparation are summarized in Table I.

Oral antibiotic therapy. Chlortetracycline, chloramphenicol, streptomycin, and oxytetracycline, in a single dose of 5 milligrams (40 mgm. per kgm.) given orally by gavage 4 hours after operation, were responsible for the survival of about half of the animals treated. No one drug was superior to another, although each was significantly more effective than no treatment at all. Since the aim of these experiments was to obtain 100 per cent survivors, further testing of the oral route of administration was abandoned.

In another experiment, neomycin given orally in combination with an intraperitoneal injection of oxytetracycline was no more effective than oxytetracycline given parenterally.

Intramuscular antibiotic therapy. When 50 per cent survival was used as the line of division, streptomycin, oxytetracycline, and the combination of penicillin and streptomycin (2.5 mgm. each) were superior to comparable doses of chlortetracycline, chloramphenicol, and penicillin. Procaine penicillin in doses up to 15 milligrams was inferior to aqueous penicillin G. Repeated doses of aqueous penicillin G, of streptomycin, or of combined penicillin and streptomycin were no more effective than single 5 milligram doses. Chlortetracycline and, to a lesser extent, oxytetracycline when given by this route had the disadvantage of producing an intense inflammatory reaction, sometimes with ensuing liquefaction necrosis of muscle. This tissue reaction probably contributed to erratic and incomplete absorption of these drugs into the general circulation. The now available intramuscular form of oxytetracycline (terramycin intramuscular) gave results comparable with those obtained when the intravenous form of the drug was used.

Intravenous antibiotic therapy. That tissue reaction at the site of intramuscular injection was a factor in the survival rate obtained with the tetracycline analogues just mentioned is reflected in the increased survival rate obtained when the experiment was repeated and the intravenous route of administration was employed: The survival rate for chlortetracycline increased from 46.6 to 86 per cent. The results with oxytetracycline—70 per cent survival with the drug given by the intramuscular route and 86.7 per cent when it was given by the intravenous route—show a similar trend. Tetracycline was less effective than either of its two analogues, oxytetracycline, and chlortetracycline.

We have no explanation for the lower survival rates obtained for the penicillin-streptomycin combination given by the intravenous route, although more rapid elimination of the antibiotics when given by this route than when given intramuscularly may be a factor. Penicillin alone and streptomycin alone gave the same results, irrespective of the route employed.

Intraperitoneal antibiotic therapy. Although the survival rates for chloramphenicol, streptomycin, oxytetracycline, and the combination of penicillin and streptomycin were essentially the same as those obtained when the same doses of drugs were given intravenously, the use of penicillin intraperitoneally effected a higher survival rate than when it was given by other routes. It is conceivable that the high local concentration which was obtained immediately following intraperitoneal injection was responsible for the improved response to the infection. In contrast, chlortetracycline injected intraperitoneally was less effective than when the drug was given intravenously. We have no explanation for the inferiority of chlortetracycline given by the intraperitoneal route over the intravenously administered antibiotic, but it may be that this agent, when given intraperitoneally, intensifies the irritative insult, thereby helping to inhibit the normal defense reactions. Tetracycline therapy was as effective as chlortetracycline, however, it was but less effective than oxytetracycline therapy.

Combined intramuscular or intravenous and intraperitoneal antibiotic therapy. In this experiment one-half of the total 40 milligrams

TABLE I.—RESPONSE TO ANTIBIOTIC THERAPY IN EXPERIMENTAL ENDOGENOUS PERITONITIS IN RATS

Therapeutic agent	Route of administration											
	Oral		Intramuscular		Intravenous		Intraperitoneal		Intramuscular or intravenous-intraperitoneal		Oral-intraperitoneal	
	S/T	% S	S/T	% S	S/T	% S	S/T	% S	S/T	% S	S/T	% S
None (controls)	3/32	9.4	33/247	13.7	22/125	17.6	10/95	10.5	19/125	14.6	6/40	15.0
1. Penicillin			36/89	43	12/29	41.4	36/60	60	34/42	76.2		
2. Streptomycin	5/9	56	77/109	71	33/45	73.3	30/40	75.0	53/68	77.9		
3. Streptomycin and penicillin			18/18	100	28/43	65.1	31/51	60.8	46/52	88.4		
4. Neomycin			75/125	58.4								
5. Chloramphenicol	18/39	46	17/31	54.8	24/35	68.7	21/39	53.9	18/30	60		
6. Chlortetracycline	15/24	64	49/105	46.6	43/50	86	19/40	47.5	42/65	64.6		
7. Oxytetracycline	4/8	50	86/124	70	30/35	85.7	42/64	65.6	68/77	88.3		
8. Tetracycline					24/40	60.0			25/42	59.8		
9. Neomycin* and oxytetracycline											52/60*	86.7

S—Number of survivors
T—Number treated
*Oral neomycin—intraperitoneal oxytetracycline

per kilogram dose was given intraperitoneally and one-half was given intramuscularly or intravenously. The results obtained by the combined intramuscular-intraperitoneal and the combined intravenous-intraperitoneal routes were so similar that they have been combined into a single column in the table. Penicillin and the mixture of penicillin and streptomycin given by the combined routes effected higher survival rates than when these drugs were given intravenously, whereas streptomycin, chloramphenicol, oxytetracycline, and tetracycline gave approximately the same numbers of survivors as when they were used intravenously. Chlortetracycline, when given by the combined routes, was less effective than when the intravenous route of administration was used.

These results may be summarized as follows:

1. With the exception of chlortetracycline, antibiotics given orally were less effective in controlling peritoneal infection in rats than when other routes of administration were employed.

2. Streptomycin, oxytetracycline, and a combination of penicillin and streptomycin gave the best survival rates for the intramuscular route. Procaine penicillin, regardless of the dosages employed, was less effective than aqueous penicillin G. Repeated injections of aqueous penicillin G or of streptomycin were no more effective than the standard 40 milligrams per kilogram single injections. Chlortetracycline, and to a lesser extent oxytetracycline, induced intense inflammatory reactions at the sites of intramuscular injection and are, therefore, not suitable for evaluating this form of therapy.

3. Chlortetracycline and oxytetracycline gave the highest survival rates for the intravenous route of administration.

4. Aqueous penicillin G was more effective when it was administered intraperitoneally than when it was given intramuscularly or intravenously.

5. The combination of penicillin and streptomycin, oxytetracycline alone, and penicillin alone effected the highest survival rates for the combined intramuscular (or intravenous) and intraperitoneal routes.

On this basis oxytetracycline and the combination of penicillin and streptomycin were selected for further studies designed to obtain insight into the mechanisms which influence the body's reaction to peritoneal infection under the influence of antibiotic therapy.

Bacteriologic studies. In an effort to achieve this objective, detailed bacteriologic analyses

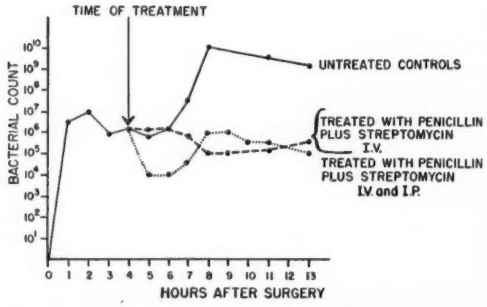
TIME OF TREATMENT
BACTERIAL COUNT
UNTREATED CONTROLS
TREATED WITH PENICILLIN PLUS STREPTOMYCIN I.V.
TREATED WITH PENICILLIN PLUS STREPTOMYCIN I.V. and I.P.
HOURS AFTER SURGERY

Fig. 1. Bacterial counts of peritoneal fluid of rats with peritonitis.

were made of the contents of the peritoneal cavity postoperatively. Cultures of peritoneal fluid were made by inoculating thioglycollate broth, eosin-methylene blue agar, and blood agar. Conventional bacteriologic procedures were used for the final identification of pure cultures. Initially, bacteriologic examinations were made at autopsy on all animals which did not survive, but the results were complicated by the fact that it was difficult to differentiate between the organisms contributing to the fatal peritonitis and those which were postmortem invaders. Accordingly, these studies were abandoned. It was thought that a better evaluation of the effectiveness of the antibiotic could be obtained by carrying out bacteriologic examinations on survivors sacrificed 72 hours after therapy was initiated. Bacteriologic identifications were often complicated by morphologic and physiologic variations, which were undoubtedly the result of antibiotic therapy.

The bacterial flora was polymicrobic in an overwhelming majority of instances. The principal aerobes recovered were Escherichia coli, 97 per cent; other coliforms (aerobacter, paracolon, proteus, and pseudomonas species), 27 per cent; micrococci, 44 per cent; streptococci, 17 per cent; gram-positive spore-forming bacilli, 18 per cent; and diphtheroids, 35 per cent. The anaerobic organisms which were recovered included clostridial species, 18 per cent; streptococci, 12.5 per cent; and bacteroides species, 6 per cent. In the treated animals which recovered, the bacterial flora of the peritoneal cavity 72 hours postoperatively was reduced both quantitatively and qualitatively. The predominating aerobe was Escherichia coli, but it was found in only 47 per cent of the treated animals as opposed to 97 per cent in the untreated controls which survived. The streptococci most frequently encountered were enterococci, 12.5 per cent in the treated animals, 5 per cent in the controls. Clostridia were found in less than 5 per cent of the treated animals and in 18 per cent of the controls. Treatment with penicillin alone or in combination with streptomycin resulted in eliminating many gram-positive organisms from the peritoneal cavity, whereas treatment with streptomycin was superior to all others in eliminating many gram-negative organisms. It was of interest to note that either penicillin or streptomycin used alone was more effective than the combination in reducing the numbers of gram-negative organisms from the peritoneal cavity.

Contrary to expectations, administration of the various antibiotics by different routes did not result in the complete elimination of any single species of organisms. Furthermore, when the ratio of survivors after 72 hours with sterile peritoneal cavities was compared to the total number of animals treated, it was found that there were no significant differences between antibiotics when the intraperitoneal, intramuscular, or intravenous routes were employed. When, however, the combined intravenous-intraperitoneal routes of administration of streptomycin or of oxytetracycline were used, there resulted significantly higher numbers of survivors with sterile peritoneal exudates. When oral neomycin plus intraperitoneal oxytetracycline was given, the ratio of survivors with sterile peritoneal cavities was equal to that obtained by streptomycin or oxytetracycline administered simultaneously, intravenously and intraperitoneally.

It was concluded from these studies that the pure taxonomic bacteriologic analysis of peritoneal exudates did not yield sufficient significant data on which to determine the comparative efficacy of therapy with the different antibiotics. Efforts were subsequently directed toward evaluation of the influence of antibiotic therapy on the total bacterial counts of peritoneal exudates by means of the agar plate count technique. One set of plates

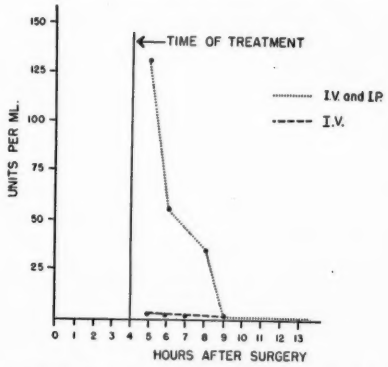

Fig. 2. Penicillin assay of peritoneal fluid of rats treated with penicillin plus streptomycin.

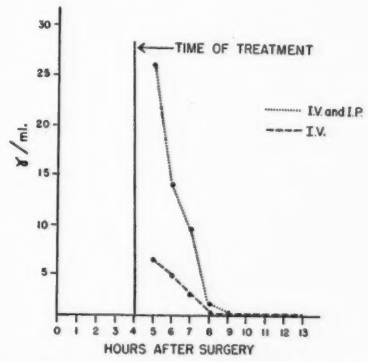

Fig. 3. Streptomycin assay of peritoneal fluid of rats treated with penicillin plus streptomycin.

was incubated aerobically and the other anaerobically, in Brewer jars. In these studies, one group of rats received penicillin plus streptomycin by the intravenous route. A second group received the same antibiotics by the combined intravenous-intraperitoneal routes, and a third group served as untreated controls. Control and treated animals were sacrificed at intervals ranging from 1 to 13 hours after operation, at which time samples of peritoneal exudate were removed for bacterial counts and antibiotic assays. Samples of blood were taken from the jugular vein for total and differential leucocyte counts. A minimum of 5 rats was in each group.

As seen in Figure 1, the total bacterial count 1 hour after surgery was 5×10^6. In the untreated controls, the count remained in the neighborhood of 10^6 for 6 hours. After this time it rose sharply to about 1×10^9, at which level it remained until the thirteenth and final hour of sampling. The counts on rats receiving a combination of penicillin and streptomycin by the intravenous route remained in the neighborhood of from 1×10^5 to 1×10^6 during the 13 hours of the experiment. The bacterial count of rats receiving the same antibiotics by the combined intravenous-intraperitoneal route showed an abrupt decrease immediately following injection of the antibiotics and rose again on the seventh postoperative hour. Explanations of these bacteria counts are more readily understood on examination of Figures 2 and 3.

When the intravenous route of administration was used, the penicillin levels of the peritoneal fluid were very low, although the streptomycin levels were at an inhibitory range for 3 hours after injection. A possible reason for the low penicillin levels is that most of the penicillin was destroyed by penicillinase elaborated by the bacteria. When the intravenous-intraperitoneal route was used, relatively large amounts of both antibiotics were present until the eighth hour. The decrease of antibiotics in this group of rats occurred concurrently with the slight rise in bacteria count. Thus it appears that the primary role of these antibiotics in the treatment of peritonitis in rats was in the prevention of bacterial proliferation to such a degree that the defense mechanisms of the body could be mobilized to combat the infection.

Hematologic studies. The hematologic studies are summarized in Figure 4. In untreated animals there was a leucocytosis immediately after the induction of the peritonitis, followed by a drop in the leucocyte count approximately 4 hours postoperatively. The leucopenia persisted until death. In the control group, studies were not continued beyond the thirteenth hour, because untreated animals were either moribund or dead after that time. It was noted that the peripheral blood of rats treated with penicillin plus streptomycin administered by the intravenous and intravenous-intraperitoneal routes was characterized by initial moderate increases in hemo-

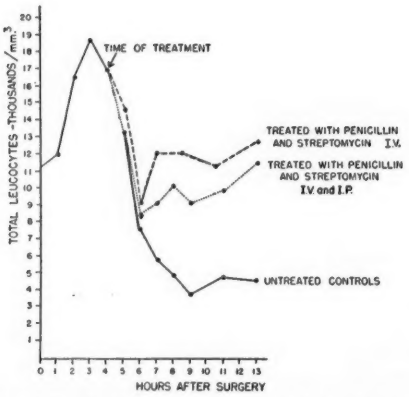
TOTAL LEUCOCYTES - THOUSANDS / mm.³
TIME OF TREATMENT
TREATED WITH PENICILLIN AND STREPTOMYCIN I.V.
TREATED WITH PENICILLIN AND STREPTOMYCIN I.V. and I.P.
UNTREATED CONTROLS
HOURS AFTER SURGERY

Fig. 4. Circulating leucocytes of rats with peritonitis.

globin concentration and erythrocyte counts, probably due to hemoconcentration, and an initial abrupt decrease in the number of circulating leucocytes. The trend toward a leucopenia was reversed 2 hours after administration of the antibiotic, and the counts were essentially normal on the thirteenth postoperative hour.

Differential counts showed that in all the rats the ratio of leucocytes remained relatively constant throughout the 13 hour test period. The average polymorphonuclear count was 83 per cent and the lymphocyte count 17 per cent. An estimated 10 to 15 per cent of the polymorphonuclears were fragmented. Stab cells, juveniles, and some myelocytes comprised 15 per cent of the polymorphonuclears counted. The majority of lymphocytes were excessively granular and 8 per cent were vacuolated. Leucocytes in the peritoneal fluid increased moderately during the first 20 hours of the disease and then rose sharply to counts of 60,000 to 80,000 per cubic millimeter at 36 hours. Counts were still about 40,000 per cubic millimeter 72 hours after surgery. It was not possible to carry out accurate leucocyte counts of peritoneal fluid during the first 15 hours after surgery because of the difficulty in distinguishing particles of mucin from leucocytes.

TABLE II.—SURVIVAL RATE OF DOGS WITH ACUTE ENDOGENOUS PERITONITIS

Route of administration	Intravenous	Intravenous and intraperitoneal
Oxytetracycline	2/10	4/10
Penicillin and streptomycin	3/10	9/10
Tetracycline	7/10	8/10
Saline controls	2/10	2/10

Key: Survivors/Treated

RESULTS IN DOGS

The results of antibiotic therapy for peritonitis in dogs are summarized in Table II and Figure 5.

Eighty dogs in which acute endogenous peritonitis was produced are included in this study. Twenty of the dogs served as controls, 20 received tetracycline therapy, 20 oxytetracycline therapy, and the remaining 20 a combination of equal amounts of penicillin and streptomycin. Half of the three latter groups were treated by the intravenous route and the other half by the combined intravenous-intraperitoneal route. All dogs were sampled periodically for 10 hours postoperatively, and then were returned to their cages where water was readily available. No attempt was made to provide supportive therapy, such as electrolyte and fluid therapy by infusion. The animals were offered food on the day following operation. After 7 days of survival they were considered recovered. Only 1 animal died after the seventh postoperative day. This was a control which died of peritonitis on the seventieth postoperative day, presumably from a mural abscess which ruptured into the peritoneal cavity.

Intravenous antibiotic therapy. When complete recovery is used as a criterion, both oxytetracycline and the penicillin-streptomycin combination were much less effective in dogs than in rats. The former drug effected a recovery rate in dogs of only 20 per cent, the latter of 30 per cent. In contrast, tetracycline administered by this route resulted in a recovery rate of 70 per cent. The average survival time was 20.2 hours for the control animals, 40 hours for the tetracycline-treated animals, 37 hours for the oxytetracycline-treated animals, and 72 hours for the penicillin with streptomycin-treated animals. Thus all antibiotics given intravenously prolonged the survival time in most dogs. At the time of autopsy examination these animals had a diffuse peritonitis.

Six additional dogs received 40 milligrams per kilogram of the penicillin-streptomycin combination at 6 hour intervals following the initial dose 2 hours after operation; their survival rate was 50 per cent. Survival time in the 3 dogs which died was the same as for the animals receiving only 1 dose of the antibiotics.

Combined intravenous and intraperitoneal antibiotic therapy. The use of oxytetracycline for these combined routes resulted in a recovery rate of 40 per cent; for tetracycline it was 80 per cent; and for the combination of penicillin and streptomycin, 90 per cent. The controls had an average survival time of 25 hours; 61 hours for the oxytetracycline-treated animals and 17 hours for the tetracycline-treated animals. The single fatality in the penicillin-streptomycin group survived 168 hours. The increase in survival rate from 30 per cent with intravenous therapy to 90 per cent for combined intravenous-intraperitoneal therapy for the penicillin-streptomycin animals is notable. Tetracycline and oxytetracycline by simultaneous intravenous-intraperitoneal administration gave essentially the same survival rates as when the drugs were administered intravenously.

Bacteriologic studies. Prior to therapy the following organisms were found in most dogs: Escherichia coli, 97.4 per cent; Clostridium perfringens, 93.2 per cent; nonhemolytic streptococci, 96.0 per cent, and Micrococcus pyogenes var. albus, 82.4 per cent. Other organisms isolated in decreasing order of frequency were gram-positive aerobic spore formers, 25 per cent, diphtheroids, 22 per cent, hemolytic streptococci, 18.6 per cent, Proteus vulgaris, 10 per cent, Aerobacter aerogenes, 6.8 per cent, and Pseudomonas species, 3.4 per cent.

The administration of antibiotics did not completely eliminate any single species of organisms during the 10 hours of the test period, although sometimes staphylococci and streptococci, while they could not be detected for 3 hours following therapy, were present again 5 and 8 hours after therapy. Mixed flora predominated during the test period and the number and ratio of the different species present varied from sample to sample. In most of the surviving animals the gram-negative organisms predominated while in the nonsurvivors the ratio of gram-positive to gram-negative organisms was increased. The peritoneal exudates of all nonsurvivors contained large numbers of bacteria, with clostridia, streptococci, micrococci, and Escherichia coli predominating. In many instances hemolytic streptococci were recovered from the peritoneal exudate at necropsy although they had not been isolated during the test period.

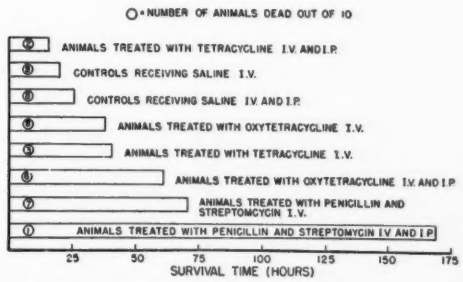
○ = NUMBER OF ANIMALS DEAD OUT OF 10
⑫ ANIMALS TREATED WITH TETRACYCLINE I.V. AND I.P.
⑩ CONTROLS RECEIVING SALINE I.V.
⑩ CONTROLS RECEIVING SALINE I.V. AND I.P.
⑨ ANIMALS TREATED WITH OXYTETRACYCLINE I.V.
⑤ ANIMALS TREATED WITH TETRACYCLINE I.V.
⑥ ANIMALS TREATED WITH OXYTETRACYCLINE I.V. AND I.P.
⑦ ANIMALS TREATED WITH PENICILLIN AND STREPTOMYCIN I.V.
① ANIMALS TREATED WITH PENICILLIN AND STREPTOMYCIN I.V. AND I.P.
25
50
75
100
125
150
175
SURVIVAL TIME (HOURS)

Fig. 5. Survival times of dogs dying from acute endogenous peritonitis.

In the dogs receiving antibiotics by the intravenous route, the total bacterial count of between 10^6 and 10^7 two hours postoperatively decreased slightly during the 10 hour test period (Fig. 6). The bacterial counts of the control group increased from a little less than 10^7 to greater than 10^8 during the same period. The total count on dogs receiving antibiotics by the combined intravenous-intraperitoneal routes showed an abrupt decrease from about 10^7 to about 10^4 within 3 hours after treatment. The counts remained at the 10^4 level in those animals treated with tetracycline and oxytetracycline while the count rose to nearly 10^5 in those animals receiving penicillin plus streptomycin.

The reasons for these bacterial count patterns are explained when Figures 7, 8, and 9 are examined. In those dogs receiving oxytetracycline and tetracycline therapy by the intravenous-intraperitoneal routes, the antibiotic levels of the peritoneal exudate remained relatively high throughout the test period and thus bacteriostasis was maintained. The curves for these two analogues are almost identical. In contrast, the antibiotic levels of the peritoneal fluid of dogs receiving penicillin plus

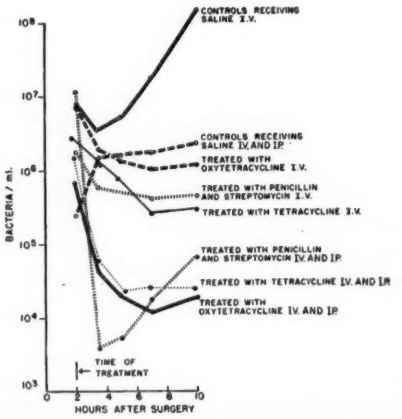
CONTROLS RECEIVING SALINE I.V.
CONTROLS RECEIVING SALINE I.V. AND I.P.
TREATED WITH OXYTETRACYCLINE I.V.
TREATED WITH PENICILLIN AND STREPTOMYCIN I.V.
TREATED WITH TETRACYCLINE I.V.
TREATED WITH PENICILLIN AND STREPTOMYCIN I.V. AND I.P.
TREATED WITH TETRACYCLINE I.V. AND I.P.
TREATED WITH OXYTETRACYCLINE I.V. AND I.P.
TIME OF TREATMENT
BACTERIA / ml.
HOURS AFTER SURGERY

Fig. 6. Bacterial counts of peritoneal fluid of dogs with experimental peritonitis.

streptomycin by the same routes decreased rapidly, after the fifth hour, and only small concentrations of either antibiotic were present 8 hours after administration. When the intravenous route of administration was used the antibiotic levels of the peritoneal fluid were considerably lower. As seen in Figure 6, intravenous administration of any of the antibiotic regimens resulted in a moderate (tenfold) and somewhat similar suppression of total bacterial counts. When antibiotics were given simultaneously by the intravenous and

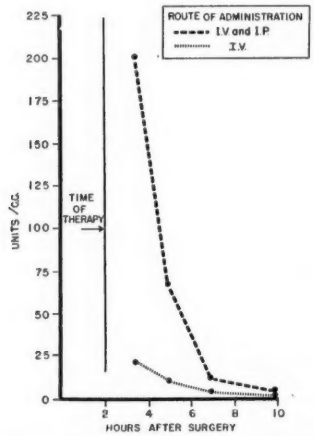

Fig. 7. Penicillin assay of peritoneal fluid of dogs treated with penicillin plus streptomycin.

the intraperitoneal routes of administration, the degree of suppression was more profound (100 fold or more). With the tetracycline compounds suppression was maintained throughout the entire test period, whereas with the penicillin-streptomycin combination there was a moderate increase in the counts after 6 hours. This increase coincided with the greatly decreased concentrations of the antibiotics in the peritoneal exudate.

Figures 10 through 13, which are representative for the 4 antibiotics assayed, indicate that the decrease of antibiotics in the peritoneal fluid and plasma can be accounted for in part by urinary excretion. In the case of all the antibiotics, excretion of antibiotics via urine was more rapid in dogs receiving intravenous therapy than in dogs receiving intravenous-intraperitoneal therapy. Likewise, plasma levels of antibiotics were higher throughout the experiment in the dogs receiving therapy only by the intravenous route. It would seem that intravenous therapy not only results in the action of less antibiotic at the focus of infection, but also that the duration of its action is shortened, as evidenced by the fact that much of the drug is rapidly excreted in the urine.

Hematologic studies. Following surgery, there was a decrease in the number of circulating leucocytes in all the dogs. The counts averaged from 15,000 to about 12,000 per cubic millimeter 3½ hours after surgery and returned to the preoperative levels 7 hours postoperatively. They increased to about 19,000 per cubic millimeter 10 hours postoperatively, except in those groups evidencing the highest recovery rates. In the control group (receiving intravenous saline) the 10 hour count was about 13,000 per cubic millimeter, and in the dogs receiving penicillin plus streptomycin by the combined intravenous-intraperitoneal routes and in those receiving tetracycline by either route the count rose to about 30,000 per cubic millimeter at 10 hours postoperatively. In all groups the differential counts of peripheral blood showed the same pattern. The ratio of polymorphonuclear leucocytes increased from about 50 per cent at the time of surgery to about 90 per cent 10 hours postoperatively, and the ratio of lym-

phocytes decreased from about 50 per cent to 10 per cent during the same period.

These results may be summarized in the following manner;

1. The bacteriology of acute diffuse peritonitis in dogs differs from that in rats in two respects: There is a greater preponderance of clostridia and of micrococci, and the total bacterial population is about tenfold greater.

2. When a single 40 milligram per kilogram dose of oxytetracycline or of penicillin with streptomycin is given intravenously, the response of the dog with peritonitis is different from that of the rat. Peritonitis in rats is usually cured by such treatment, whereas peritonitis in dogs is not, although the time of survival of dogs after operation is prolonged beyond that of treated controls. When repeated doses of the penicillin-streptomycin combination are given, the number of survivors tends to increase. Penicillin with streptomycin given by both the intravenous and intraperitoneal routes simultaneously results in a high survival rate in both species.

3. Tetracycline is more effective in acute diffuse peritonitis in the dog than in the rat, whether the antibiotic is given intravenously or by combination intravenous and intraperitoneal administration. Inasmuch as the antimicrobial spectrum of tetracycline is the same as that of the analogue oxytetracycline, we postulate that oxytetracycline is more toxic than tetracycline for the dog with acute peritonitis. The degree of bacterial suppression, and the plasma and peritoneal exudate levels obtained are similar for both compounds.

4. As in the rat, no single microbial species is completely eliminated from the peritoneal exudate by antibiotic therapy. Recovery is associated with suppression of the total bacterial flora to a level commensurate with survival of the animal.

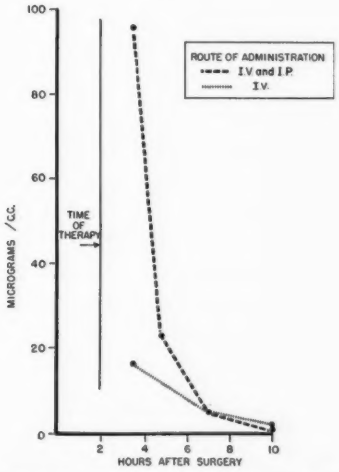

Fig. 8. Streptomycin assay of peritoneal fluid of dogs treated with penicillin plus streptomycin.

DISCUSSION

Because of the well known defensive powers of the peritoneum, the production of lethal, acute, septic peritonitis in the laboratory animal is difficult. As shown by Steinberg, intraperitoneal injections of cultures of bacteria seldom produce peritonitis. Small numbers of micro-organisms in the peritoneal cavity may be destroyed by phagocytosis, whereas very large inocula result in a transient and varying degree of peritoneal reaction, septicemia, and death. To produce peritonitis, bacteria of great enough virulence and of sufficient numbers must be retained in the peritoneal cavity. Devitalized tissues and foreign substances, such as feces, gastroduodenal contents, bile, and blood tend to hold the bacteria. In our standardized preparations in the rat and in the dog, a suspension of hog mucin was employed to hold the fecal bacteria in the peritoneal cavity for the production of a lethal, diffuse peritonitis.

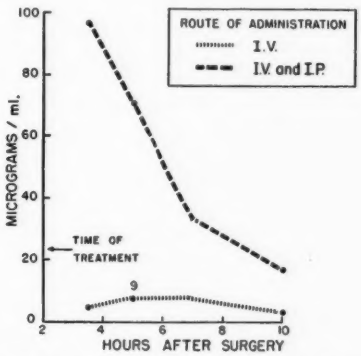

Fig. 9. Tetracycline assay of peritoneal fluid of dogs with experimental peritonitis.

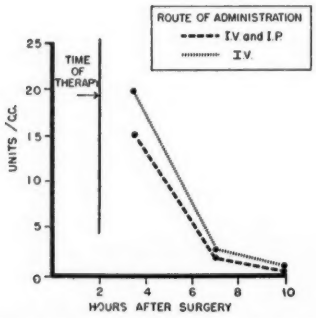

Fig. 10. Penicillin assay of plasma of dogs treated with penicillin plus streptomycin.

Investigations of bacterial flora of acute endogenous peritonitis have disclosed several observations upon which there is more or less general agreement.

1. In most instances the exudate contains numerous species of aerobic and anaerobic bacteria. In Altemeier's (1) series 3 to 7 types of organisms, representing 16 different species of aerobes and 18 of anaerobic micro-organisms, were recovered in peritonitis of appendiceal origin. The aerobic species include gram-negative enteric bacilli, hemolytic and nonhemolytic streptococci, other micrococci, diphtheroids, and gram-positive sporulating bacilli. Among the anaerobes are: Clostridium perfringens and other less frequently encountered clostridial species, bacteroides species, anaerobic streptococci and micrococci, and anaerobic gram-negative bacilli. The proportions of isolated mixed flora vary considerably in different animal species.

2. The majority of the clostridia, anaerobic streptococci and micrococci, and bacteroides species are susceptible to penicillin and the tetracycline analogues and resistant to streptomycin and neomycin. The gram-negative species are frequently penicillin-resistant and penicillinase-producing, but are frequently susceptible to streptomycin, neomycin, chloramphenicol, and the tetracycline compounds.

3. A definite synergistic or cumulative pathogenic action of these organisms growing in symbiosis has been demonstrated in experimental animals by Altemeier (1), Meleney, and Hite. The mixtures are more lethal in quantities which are considerably less than pure cultures of the components of the mixture. The greater the number of bacterial species which are contained in the exudate, the greater the severity of the infection is likely to be.

4. One characteristic of the anaerobic flora is the ability to attack and break down tissue proteins with the release of enzymes and toxins which combat the attempts of the body defenses to wall off the infection, as van Heyningen has shown. For example, toxins elaborated by clostridia include alpha toxin, which is proteolytic, hemolytic, and lethal. Substances elaborated by other gram-positive organisms include leucocidins, fibrinolysins, and hyaluronidase, which favor dissemination of the infection. In the process of tissue breakdown the anaerobes produce various foul odors erroneously attributed to Escherichia coli. The gram-negative bacillary flora contribute to the morbidity of the disease process by the elaboration of fibrinolysins and endotoxins. In addition, they produce penicillinase and are resistant to the action of penicillin except in high concentrations of the drug (15). Because of this action penicillin was originally considered to be contraindicated in peritonitis therapy.

The toxic substances elaborated by bacteria in peritoneal exudates undoubtedly contribute materially to the alterations in hemodynamics and the metabolic alterations observed in the course of the disease. These changes are systemic reflections of the local disease. They are important, but they do not reflect the essential factors in this infection. Thus, Tanturi has shown that whereas early surgical removal of the focus of infection, which is the fundamental principle in surgical therapy of peritonitis, eventuates in a high recovery rate from an otherwise lethal infection, late surgical intervention does not.

On the other hand, measures directed solely toward increasing tolerance to the shock-producing factors of the disease have not been very fruitful. Orr and Haden noted a fall in blood chlorides and a progressive rise in urea and nonprotein nitrogen in acute peritonitis in dogs. Blalock found that the intravenous administration of saline solution in dogs with

experimental peritonitis caused a marked increase in peritoneal exudate, while subcutaneous administration did not; the mortality rate was not influenced by saline therapy. Kingsley and Terzian found that experimental peritonitis in dogs caused a significant decrease in reactivity of serum globulin. No significant change occurred in the serum albumin biuret activity or total nitrogen activity. These authors suggested that the degree of loss of biuret nitrogen in serum globulin could be due, in part, to the rapid loss of large amounts of circulating plasma protein, which placed an additional burden on a liver already actively involved and impaired by the toxemia of the infection. Ebert and associates found that untreated dogs with peritonitis rapidly developed shock characterized by a decrease in arterial pressure, hemoconcentration, low plasma volume, and a fall in cardiac output. The average reduction in plasma volume was 44 per cent. After death, 350 to 550 cubic centimeters of fluid with an average protein content of 2.5 grams was found in the peritoneal cavity. Transfusion therapy did not prolong life. In our studies, examination of the peritoneal cavity of rats dying from peritonitis revealed the presence of 4 to 8 milliliters of exudate, which represents a significant proportion of the total plasma volume of the animal.

Tanturi isolated a number of enzymes and toxins in the peritoneal exudate of dogs with acute diffuse peritonitis. Among these was lecithinase, one of the lethal factors of Clostridium perfringens. If the appendix was isolated from the peritoneal cavity by a watertight polyethylene sac, the majority of animals survived an otherwise lethal infection. Commercial gas gangrene antitoxin did not inhibit the lecithinase production by the Clostridium of the dog. It is apparent that a direct action on the bacteria is the determining important factor in survival from an otherwise lethal peritoneal infection.

The influence of antibiotic therapy on the course of experimentally induced acute septic peritonitis has been studied extensively. Fauley and associates in 1944 were the first to report that otherwise lethal peritonitis in dogs could be controlled, with survival of the animals, when aqueous penicillin G in a dosage

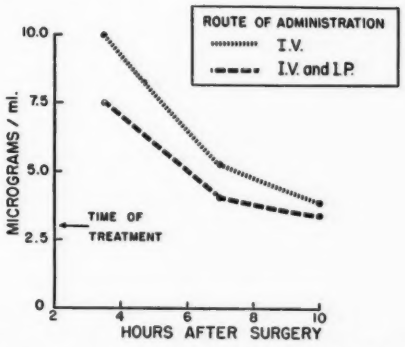

Fig. 11. Tetracycline assay of plasma of dogs with experimental peritonitis.

of approximately 4 milligrams per kilogram of body weight per day was administered intramuscularly at 4, then 8 hour intervals for 8 days. When, however, an internal fecal fistula occurred and the bowel contents continuously flooded the peritoneal cavity, or when treatment was delayed for 12 hours, the survival rate was reduced significantly. Crile emphasized the need for large doses of penicillin in human acute bacterial peritonitis and supported this contention by demonstrating that, in vitro, staphylococci in the presence of Escherichia coli were inhibited only when 8 times as much penicillin was present as was needed when the staphylococcus was present in pure culture. Altemeier (2) showed that the increased penicillin requirement for penicillin-susceptible organisms in mixed cultures was due to the elaboration of penicillinase by gram-negative enteric bacilli. Rothenberg and associates confirmed these observations. They found that whereas divided doses of 100,000 (60 mgm.) or 200,000 (120 mgm.) units of aqueous penicillin G per day for 6 days effected survival of some dogs with acute bacterial peritonitis, all the treated animals survived only when they received 500,000 units (300 mgm.) of penicillin daily for 6 days. These investigators attributed survival to partial or complete elimination of the penicillin-susceptible gram-positive micro-organisms from the peritoneal exudate. Vernetti and Ligas showed that in the acute perforative appendiceal peritonitis of rabbits, penicillin by the intraperitoneal route was more effective

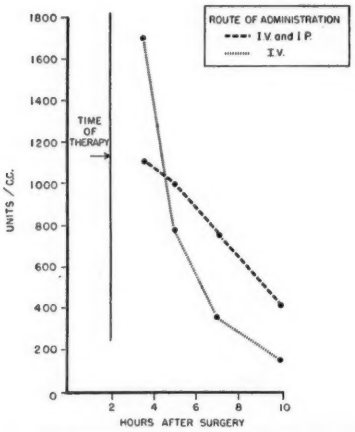

Fig. 12. Penicillin assay of urine of dogs treated with penicillin plus streptomycin.

than by the intravenous route, dose for dose. The importance of the dosage form of penicillin is reflected in the studies of Barbieri and associates, who noted a cure rate of only 20 per cent in dogs with peritonitis which were given a suspension of procaine penicillin intramuscularly in a dosage of 13,000 units (about 8 mgm.) per kilogram per day.

It is apparent from these and other studies that the responses of peritonitis to penicillin therapy vary with the severity of the infection induced, the dosage of penicillin, the dosage form of the drug administered, and the route of administration. Our own studies in endogenous peritonitis in the rat confirm the earlier observations that aqueous penicillin G is superior to procaine penicillin G, and that intraperitoneal injection of aqueous penicillin is more efficacious than intramuscular or intravenous administration of the antibiotics.

When streptomycin became available, it was investigated for its effects on acute bacterial peritonitis, because of its activity against many micrococci and most gram-negative enteric organisms. In experimental peritonitis in dogs, Murphy, Zintel, and Rothenberg and their associates found that streptomycin therapy was distinctly inferior to penicillin therapy. Rothenberg and his group noted that if 4.0 grams of streptomycin were injected intraperitoneally into their dogs, cultures of 3 of the 4 animals were sterile at autopsy. This dosage is within the lethal range. In the experimental closed loop appendicitis of rabbits, however, Farris and Romack reported excellent results with streptomycin therapy. Vernetti and Ligas, who also employed rabbits, found streptomycin inferior to penicillin; the best survival rates obtained followed combined penicillin-streptomycin therapy. In our studies of the comparative effects of antibiotics in experimental peritonitis in rats, streptomycin was superior to penicillin, dose for dose, except when the latter agent was injected intraperitoneally. The marked differences in reponse obtained with streptomycin in rabbits and rats, on the one hand, and in dogs on the other, are probably related to the differences in proportions of anaerobic bacterial flora present in the dog and in the smaller animals, and the relative resistance of these micro-organisms to streptomycin. In the dog we found combined intravenous-intraperitoneal therapy with the penicillin-streptomycin mixture superior to intravenous therapy.

The tetracycline analogues, chlortetracycline and oxytetracycline, and more recently tetracycline, are unique in that they inhibit many of the species of gram-positive and gram-negative organisms associated with acute bacterial peritonitis. They are absorbed into the general circulation whether given orally or by injection. Chloramphenicol has similar properties but is less effective in vitro, weight for weight, than the tetracycline compounds. In treating experimental peritonitis in the dog, Schweinburg and his associates (18, 19) and Yeager and his group reported excellent survival rates with the tetracycline drugs given orally preoperatively and postoperatively, but in neither case were the rates superior to intramuscular penicillin therapy. Schweinburg and Barbieri and their associates found that chlortetracycline by the intravenous route was less effective than by the oral. Schweinburg noted further that chlortetracycline resulted in deaths in 2 daily intravenous doses of 400 to 1,200 milligrams which he attributed to drug toxicity. Prolonged intraperitoneal therapy also resulted in death, but when this route was employed for only 2 days, the recovery

rate was 80 per cent. Both these groups of investigators observed that the bacteria which were sensitive to the antibiotic used in treatment were frequently found in terminal cultures. Schweinburg concluded that the superiority of the oral route was not due to the action of the absorbed fraction upon the intraperitoneal process, but to the rapid suppression of the pathogenic potential of the intraintestinal bacteria which continue to contaminate the peritoneum after the initial trauma to the appendix has been produced.

Schatten and Abbott compared intraperitoneal and intravenous oxytetracycline therapy in experimental peritonitis in dogs and found that the intraperitoneal therapy was distinctly superior to the intravenous route of administration. They believed that the markedly high levels of oxytetracycline that occurred in the peritoneal fluid following the intraperitoneal administration of each dose, as well as the diffusion of the concentrated oxytetracycline throughout the peritoneal cavity, were responsible for the almost complete elimination of pathogenic organisms from this region in dogs treated with oxytetracycline intraperitoneally. Regardless of the method of therapy, death occurred within 96 hours in all dogs from which gram-positive cocci (and clostridia) were isolated from the peritoneal fluid after therapy was instituted.

In our studies on peritonitis in the rat, the tetracycline compounds given intravenously effected high survival rates. Intraperitoneal therapy was less effective, and combined intravenous-intraperitoneal therapy was no better than intravenous therapy alone. In the dog, on the other hand, tetracycline by the intravenous route was superior to oxytetracycline. It may be that the former compound is less toxic to the dog with peritonitis than is oxytetracycline, since antibacterial activity of both compounds is comparable. The reasons for the discrepancies in results with these 2 tetracycline analogues have not been finally determined. The combined intravenous-intraperitoneal route of administration of oxytetracycline in dogs was better than the intravenous, which is in agreement with the observations of Schatten and Abbott. Combined intravenous-intraperitoneal therapy results in a greater suppression of bacteria in the peritoneal exudate than does intravenous therapy. Our findings are in agreement with others in that organisms sensitive to the tetracycline compounds can be recovered in cultures of the peritoneal cavity in the presence of bacteriostatic concentrations of the drugs in the peritoneal exudate. Recovery from the infection appears to be commensurate with suppression of the total bacterial count of the peritoneal exudate to approximately 10^5 organisms per milliliter.

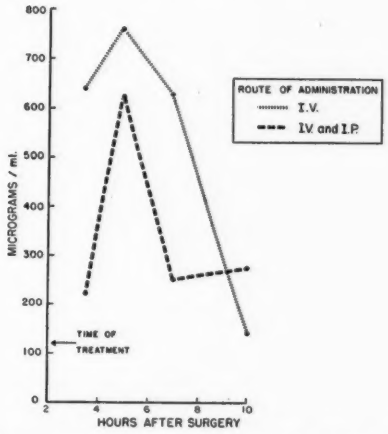

Fig. 13. Tetracycline assay of urine of dogs with experimental peritonitis.

In general, the over-all responses to antibiotic therapy support the contention that the gram-positive flora of peritonitis plays the dominant role in the morbidity of the disease. Once these are brought under control, the body defenses apparently are able to cope with the remaining gram-negative bacillary flora. To test the validity of this hypothesis, a series of rats which survived the disease was sacrificed at intervals after operation and the aerobic bacterial flora of the exudate analyzed. The results are presented graphically in Figure 14. The abscissa represents the percentage of animals from which gram-positive or gram-negative bacteria were isolated, and the ordinate the days on which the animals were sacrificed for study. It will be noted that up to 4 days postoperatively there was heavy colonization of the peritoneal cavity by a mixed flora of micro-organisms. Gram-nega-

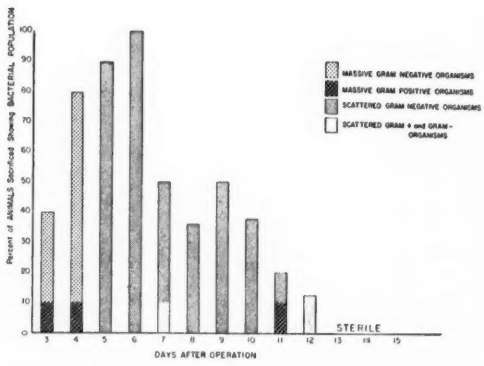

Fig. 14. Aerobic bacterial population of peritoneal cavity following cecal incision for experimental peritonitis sacrificed survivors.

tive bacilli continued to be isolated through the fifth day, though in small numbers, and only an occasional gram-positive organism was recovered. Some animals continued to harbor gram-negative bacilli from the seventh to the tenth day. Mixed organisms could be recovered from the neighborhood of the healing cecal wound on the eleventh and twelfth days. Thereafter the peritoneal cavity was sterile. It should be borne in mind that as absorption of exudate was taking place, the height of these columns is not strictly comparable, one with the other.

SUMMARY

A standardized acute diffuse peritonitis in the rat and dog was produced by operative perforation of the cecum followed by intraperitoneal injection of a suspension of hog mucin. The mortality was 86 per cent for rats about 24 hours after operation and 80 per cent for dogs. Controlled trials were made of the different antibiotics, administered by various routes, in treatment of peritonitis. The trial drugs were administered in a single dose of 40 milligrams per kilogram of body weight. No additional therapeutic or supportive measures were employed during these trials.

A total of 1,714 rats were employed for the antibiotic trials, and an additional 664 served as untreated controls. Eighty-six dogs were studied, 20 of which served as untreated controls. The clinical criterion of effectiveness of antibiotic therapy was complete recovery from the disease. In dogs, prolongation of survival time was also noted.

In rats, chlortetracycline given orally was the only antibiotic which was more effective by this route than by parenteral administration, although the group treated orally in general progressed more favorably than the controls. Comparison of the relative efficacy of the different antibiotics given by intramuscular injection is hampered by the fact that suitable dosage forms of all the antibiotics are not available for this route of administration. When the antibiotics were given to rats intravenously, chlortetracycline and oxytetracycline gave the highest survival rates, followed by streptomycin, chloramphenicol, a combination of penicillin and streptomycin, and penicillin alone. Intraperitoneal therapy was less effective than intravenous therapy, except when penicillin was used. Combined parenteral and intraperitoneal therapy was more effective than parenteral therapy alone in the instance of penicillin with streptomycin and with penicillin alone. This form of therapy was no better than parenteral therapy with oxytetracycline, chloramphenicol, or streptomycin, and was inferior to parenteral therapy with chlortetracycline. The inferiority of chlortetracycline by the intraperitoneal route might be explained by its possible toxic effects rather than by its antibacterial qualities. Although none of the antibiotics tested regularly eliminated any single species of micro-organisms, successful antibiotic therapy was always associated with a continued suppression of the total bacterial count to about the level of the inoculum present at the time the infection was induced. The critical level appears to be 1×10^5 organisms per milliliter of exudate. When this level was exceeded by a hundredfold or more, the animals died. The peritoneal cavity continued to harbor micro-organisms for days after apparent recovery from the disease. Gram-positive organisms were eliminated first, then the gram-negative bacilli, and cultures finally became sterile about 2 weeks after operation.

In dogs, the combination of penicillin and streptomycin and of oxytetracycline and tet-

racycline were compared when administered by the intravenous and the intravenous-intraperitoneal routes. When tetracycline was employed, the survival rates for the intravenous route were similar to those obtained in the rat, but were distinctly inferior when oxytetracycline or the combination of penicillin and streptomycin was given. These differences in therapeutic responses are probably related to the dissimilarities of the bacterial flora of peritonitis in the two animal species. The reason for the difference in survival rates with the two biologically similar compounds, oxytetracycline and tetracycline, is not understood, but drug toxicity may be a factor. The favorable results for the penicillin-streptomycin mixture followed the combined intravenous-intraperitoneal routes of administration. Contrary to expectations, the penicillin-streptomycin mixture was the only antibiotic which seemed to promote a more favorable outcome when given simultaneously by the intravenous and the intraperitoneal routes. Survival was accompanied by a decrease in the total bacterial count of the peritoneal exudate and a reduction in the number of gram-positive organisms recovered in both animal species. Concomitantly the number of circulating leucocytes in the peripheral blood was increased.

It would also appear from these observations that the mechanism of action of antibiotics in the therapy of peritonitis is the suppression of the total bacteria in the peritoneal exudate to such a degree that the defense mechanisms of the body can cope with the surviving bacteria. This suppression must be effected, however, before the toxic substances elaborated by the micro-organisms produce lethal intoxication.

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LEAKAGE OF THE DUODENAL OR ANTRAL STUMP COMPLICATING GASTRIC RESECTION

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THE problem of safe closure of the duodenal stump has been foremost in the minds of surgeons since the Billroth II type of gastric resection and its modifications came into use. The complication of duodenal leakage is not rare and is one of the major causes of mortality in gastric resections. In the present article are presented 11 cases of duodenal stump leakage and 2 cases of antral stump leakage, proved by autopsy, secondary operation, or by development of an external bile fistula. The reason for this complication, its pathologic physiology, diagnosis, and management are discussed as well as methods of prevention.

MATERIAL

Thirteen cases of stump leakage occurring from 1937 through 1951 at the Boston City Hospital are presented.

In reviewing 621 available records of gastric resections of all types in which a duodenal or pyloric stump was present, 13 cases of leakage from the stump were discovered, for an overall incidence of 2.1 per cent. In 2 of these cases, the ulcer was excluded and a portion of the gastric antrum was left behind to obtain an adequate cuff for closure (Cases 10 and 11).

One case of duodenal stump leakage followed total gastrectomy for gastric carcinoma (Case 9). If the two procedures with antral stump dehiscence are excluded, an incidence of 1.8 per cent duodenal stump leakage is obtained. The actual incidence is probably higher, but only proved cases have been included in this study.

Ten of the 13 patients reported died as a direct result of stump dehiscence, giving a mortality of 77 per cent.

One patient had carcinoma of the stomach. In the remaining 12 patients diagnosed as having duodenal ulcer, the major complication leading to operation was obstruction in 5, bleeding in 6, and intractable pain in 1. Many of these patients had more than one complication.

The 12 patients with duodenal ulcer had symptoms ranging from 4 years to 26 years with an average of 12 years. The patient with gastric cancer had symptoms for 3 months.

Operations. The operation was done as a surgical emergency for massive bleeding in only 1 instance (Case 4). The stump closure was noted to be difficult because of scarring and inflammation about the ulcer site in 6 cases of duodenal ulcer (Cases 1 through 6) and presented no technical difficulty in the remaining cases.

Leakage from the duodenal or antral stump occurred (as far as can be determined from the clinical course) from the first to the eighth postoperative days in all but 2 cases when it occurred late on the seventeenth and forty-first day, respectively.

Diagnosis. The diagnosis of stump dehiscence was made or suspected early in 3 cases and late in 7 cases. In 3 cases the diagnosis was not mentioned in the clinical record prior to autopsy (Cases 5, 12, and 13). In these 3 cases, generalized peritonitis was the primary result of the dehiscence, and although the average duration of survival following onset of leakage was 3.3 days, no secondary operation was performed. Each of these cases exhibited classical signs of peritonitis, with abdominal tenderness and spasm, absent peristalsis, and leucocytosis. In addition 1 of these patients became icteric. This failure in diagnosis has also been noted by Bartlett and Lowell and by Larsen and Foreman.

PATHOGENESIS OF DUODENAL LEAKAGE

The incidence of duodenal leakage is not statistically altered by an open or closed

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technique of stump closure. Mobilization of over 2 centimeters of cuff for duodenal closure may impair the blood supply to the stump, so that necrosis and leakage occur. Steinberg in 1940 cited as causes of duodenal dehiscence inclusion of inflammatory tissue in the suture line, devitalization of tissue by crushing clamps, digestive action of pancreatic juice liberated in the vicinity of closure, and ligation of major arteries nourishing the duodenal tissues. Others have incriminated the presence of a drain near the suture line of the duodenum, trauma, and sepsis in producing duodenal necrosis.

In addition to these local factors, Bartlett and Lowell have called attention to general systemic factors such as anemia, hypoproteinemia, and dehydration as obviously affecting the healing of the sutured duodenum.

Obstruction at the stoma has long been recognized as a factor in duodenal stump blowout. Obstruction in the proximal jejunal limb was indicated by McNealy and others. Normally, intraduodenal pressure varies up to 15 centimeters of water. This is higher during periods of increased peristaltic action, particularly during reversed peristalsis which is a normal phenomenon in the duodenum. The duodenal suture line is subject, therefore, to greater stress than the gastrojejunostomy.

There is little question that leakage from the duodenal stump is due in most cases to a combination of these factors. However, we believe, from a study of the records, that one factor is usually paramount. In this series, therefore, we have attributed 6 cases to local factors, 3 to systemic factors, and 4 to obstruction distal to the suture line.

Local factors. The 6 cases (Cases 1 through 6) included in this category are outlined in the following. Four cases represent exteriorization procedures, namely, transection and closure of the duodenum at the ulcer site and exteriorization of the ulcer from the duodenal lumen. In Case 5 the ulcer was excluded and in Case 6 it was removed. These patients all had scarred posterior penetrating ulcers. The closure of the duodenal stump was formidable in each instance. All developed duodenal leakage within 5 days following operation. Only 1 in this group recovered.

CASE 1. A 27 year old white male (BCH 1205873) was admitted to the hospital March 27, 1946, after vomiting blood for 2 days. Vomiting after meals started 8 months prior to entry. Hematemesis occurred 7 months, and perforation 6 months, prior to admission. With hospitalization, bleeding stopped and a gastrointestinal x-ray series showed 90 per cent retention at 6 hours. Following a recurrent bout of hematemesis while in the hospital, subtotal gastric resection was performed on April 20, 1946, and a scarred, posterior penetrating ulcer was found just beyond the pylorus. Because of difficulty encountered in dealing with the duodenal stump, the duodenum was transected at the ulcer site and the ulcer was exteriorized. An antecolic Polya anastomosis was performed.

On the third postoperative day the patient developed a temperature of 102 degrees F., with a distended quiet abdomen and slight jaundice. The following day the wound drained duodenal contents. The patient was, therefore, treated supportively with the expectation that the process would localize and a fistula would form. However, following a septic course he expired on the eighth postoperative day.

Autopsy revealed a generalized peritonitis due to a ruptured duodenal stump.

CASE 2. A 29 year old white male (BCH 1138986) was admitted to the hospital March 31, 1944 complaining of epigastric pain and vomiting for 1 month and passage of tarry stools for 2 weeks. There was a 7 year history of epigastric pain, with x-ray evidence of duodenal ulcer. The patient had been hospitalized 4 years prior to this admission for hematemesis, and 2 years previously for perforation.

After 2 weeks' hospitalization the patient vomited 200 cubic centimeters of blood. Operation on April 14, 1944 revealed a scarred, posterior penetrating ulcer in the second portion of the duodenum. The duodenum was transected at the ulcer site and the ulcer was exteriorized. Subtotal resection was done and an antecolic Hofmeister anastomosis was performed.

On the first postoperative day the patient was hyperpyretic (103 degrees) and developed a left hydrothorax and left lower lobe pneumonia. During the next several days the abdomen became distended. He was given supportive therapy and after a stormy course an exploratory laparotomy was performed on the twelfth postoperative day. A generalized peritonitis with a leaking duodenal stump was found. The stump was drained and the patient recovered in 8 weeks when drainage ceased spontaneously.

CASE 3. A 45 year old white male (BCH 932927) was admitted to the hospital March 10, 1939, one hour after he vomited about a quart of blood. There was a history of perforation 15 years prior to entry, epigastric pain for 5 years, and hematemesis with obstruction proved by x-ray examination 1 year previously.

On admission the patient was in shock but responded to a medical regimen including blood transfusions. In the fifth hospital week he had recurrent

hematemesis and developed almost total pyloric obstruction. Because of his poor condition, a jejunostomy was performed for feeding purposes, and blood chemistry including nonprotein nitrogen, serum chlorides, and carbon dioxide combining power were restored to normal. On May 19, 1939 operation was performed and a markedly scarred, penetrating ulcer 3 centimeters in diameter was found in the first portion of the duodenum. The duodenum was transected at the ulcer site and the ulcer was exteriorized. Several suture ligatures were required to control hemorrhage from the ulcer site and pancreas. Subtotal gastric resection with a retrocolic, Hofmeister anastomosis was carried out.

Postoperatively, the patient developed a left lower lobe pneumonia on the first day, which cleared with treatment over the next several days. On the fifth postoperative day he developed generalized abdominal pain and a temperature of 101 degrees F. On the tenth postoperative day, a subphrenic abscess was surgically drained, and a duodenal fistula developed. Following this the patient improved, but on the twenty-sixth postoperative day, during a chest tap for left hydrothorax, he aspirated vomitus and expired suddenly.

Autopsy revealed a duodenal dehiscence and fistula, and the presence of aspirated gastric contents in the bronchial tree.

CASE 4. A 48 year old white male (BCH 934618) was admitted to the hospital March 25, 1939 shortly after vomiting about 1½ pints of blood and fainting. One week previously he had been placed on a milk and cream diet by his family doctor for epigastric pain which had been present, intermittently, for 15 years.

On admission the patient was not in shock and had a red cell count of 3.5 million. Following 2 additional bouts of hematemesis on the third and fifth hospital days, an emergency gastric resection was performed. A posterior penetrating ulcer in the second portion of the duodenum was found to have eroded into the gastroduodenal artery. Bleeding was controlled with multiple suture ligatures, and the duodenum was closed by a modified Nissen technique 2 centimeters above the ampulla of Vater. A drain was placed near the duodenal stump prophylactically, and a subtotal resection with antecolic Polya anastomosis was performed.

Postoperatively, the patient developed a temperature of 104.5 degrees F. and died in 12 hours with pulmonary edema.

Autopsy disclosed necrosis of the duodenal suture line with duodenal leakage and generalized peritonitis.

CASE 5. A 55 year old white male (BCH 1139230) entered the hospital April 3, 1944 because of continuous vomiting of 5 days' duration. There was a history of perforated ulcer 4 years previously.

In the hospital the patient responded well to medical treatment and a gastrointestinal x-ray series during the second hospital week disclosed a chronic duodenal ulcer with evidence of obstruction.

At operation on April 14, 1944 a duodenal ulcer with considerable scarring and surrounding inflammation involving the common duct and the pancreas was found. The ulcer was excluded and the duodenal stump closed with "marked difficulty." A subtotal gastrectomy with an antecolic Hofmeister anastomosis was then performed.

Postoperatively, the patient developed a left lower lobe pneumonia with a temperature of 101 degrees F. on the second day. He complained of chest pain, became disoriented, icteric, and by the fifth postoperative day developed a classical peritonitis with hyperpyrexia (105 degrees F.). Within a few hours the patient became hypotensive and died.

Autopsy disclosed a leaking duodenal stump with necrosis at the suture line, generalized peritonitis, and bilateral hydrothorax.

CASE 6. A 39 year old white male (BCH 1351638) was admitted to the hospital February 26, 1950, complaining of epigastric pain of 5 months' duration. Intermittent attacks of pain first started 5 years previously, but had always been relieved by amphojel or milk. Gastrointestinal x-ray studies performed 3 years previously revealed a duodenal ulcer. There was no history of bleeding, perforation, or obstruction. In the 5 months prior to admission, relief of epigastric pain was not afforded by medical treatment.

In the hospital medical treatment was more successful. Gastrointestinal x-ray studies revealed a chronic duodenal ulcer.

Operation on March 4, 1950, disclosed a markedly scarred posterior penetrating ulcer in the second portion of the duodenum. A subtotal gastrectomy with antecolic Hofmeister anastomosis was performed and the ulcer removed. A small portion of pancreatic capsule was removed with the ulcer, and several silk sutures were used to close the defect in the pancreas. A rubber drain was placed near the duodenal stump and brought out through the wound.

Postoperatively the temperature spiked to 104.6 degrees F. on the second day, with a pulse of 146 and respirations 40. Urinary diastase determination was reported 1,700 units. A chest film showed increased density at the base of the right lung with a splinted right hemidiaphragm. At this time a diagnosis of pancreatitis and right lower lobe atelectasis was entertained. The wound began to drain serosanguineous fluid on the second day which became gradually bile stained and digested the skin of the abdominal wall. On the seventh postoperative day the patient was first noted to be jaundiced. By the tenth day it became apparent that the efferent loop was obstructed because of the large quantities of bile-containing material which were aspirated from the stomach daily. Despite these losses the patient's electrolytes were maintained at normal levels by vigorous therapy.

On the eleventh postoperative day, a laparotomy was performed and the efferent jejunal loop was found adherent to an inflammatory mass surrounding a duodenal cutaneous fistula. At this point the

efferent loop was kinked and obstructed. The adhesions were lysed and the abdomen drained.

Two days after this operation the patient became oliguric, the temperature rose to 105.8 degrees F. (rectal), and he expired.

Autopsy permission was not granted.

Systemic factors. In the 3 cases included in this category (Cases 7, 8, and 9), the poor condition of the patient was the most important factor leading to duodenal stump dehiscence. One patient had a gastric cancer, 1 a small ulcer in the first portion of the duodenum, and in 1, only scarring of the duodenum was found.

No technical difficulty in closing the duodenal stump was encountered in these cases. Duodenal dehiscence occurred on or after the fourth day in all 3. There were 2 deaths and 1 recovery.

CASE 7. A 34 year old white male (BCH 1360366) was admitted to the hospital May 17, 1950 with a complaint of vomiting and loss of 15 pounds in weight over a 3 month period. Two days after admission gastrointestinal x-ray examination revealed almost complete obstruction. Blood chemistry studies prior to operation disclosed a nonprotein nitrogen value of 92 milligrams per cent, a carbon dioxide combining power of 79 volumes per cent, and a chloride level of 79 milliequivalents per liter.

At operation on June 1, 1950, a small anterior ulcer was found 2 centimeters distal to the pyloric ring in the duodenum. The ulcer was removed and the duodenal stump closed without difficulty. A subtotal gastrectomy with an antecolic Polya anastomosis was performed.

Postoperatively, the patient ran a spiking temperature from the second day. On the fifth day he developed sudden epigastric pain accompanied by a drop in blood pressure to 80/60 and a rigid, tender, and silent abdomen. On the next day emergency laparotomy was performed and a drain placed in the right upper quadrant. The patient developed a left empyema and died on the ninth postoperative day.

Autopsy disclosed a generalized peritonitis, due to rupture of the duodenal stump. In addition there was a left empyema and right hydrothorax.

CASE 8. A 27 year old white male (BCH 1410460) was admitted to the hospital on June 9, 1950 with a complaint of hematemesis of 1 day's duration. The patient had 3 similar episodes of hematemesis requiring hospitalization during the previous 2½ years. On his last admission in November 1948, a duodenal ulcer had been diagnosed by roentgenologic studies. Blood studies on this present admission revealed a hemoglobin of 8 grams per cent. The patient was transfused with whole blood and prepared for operation. At operation on June 20, 1950 only scarring in the anterior wall of the second portion of the duodenum was found. The scarred area was removed, the duodenal stump closed, and subtotal gastric resection with antecolic Hofmeister anastomosis was performed.

Postoperatively, the patient did well until the eighth day when he developed pain and tenderness in the left upper quadrant, with a temperature of 101 degrees F. On the fifteenth day hematemesis and melena recurred which responded to blood transfusions and supportive therapy. Because of a persistent temperature elevation (101 to 103 degrees F.), however, and an elevated left hemidiaphragm, an exploratory laparotomy was performed on the twenty-fifth postoperative day and a large collection of blood clot, bile, and pus was drained from the duodenal stump region. Ten days later a subphrenic abscess drained spontaneously through the wound. The resulting duodenal fistula was complicated by fecal drainage and ultimately required surgical closure.

On a later admission, a diagnosis of pseudohemophilia with atypical fibrinogenopenia was finally established.

CASE 9. A 65 year old white male (BCH 1321939) entered the hospital on May 11, 1949 complaining of epigastric pain after meals, of 3 months' duration. There was a history of progressive anorexia, weakness, and weight loss with intermittent hematemesis and melena for 2 months. On admission the patient could neither stand nor sit upright without convulsing, a result of anemic cerebral hypoxia combined with old cerebrospinal syphilis. Gastrointestinal x-ray examination revealed a gastric tumor. The patient was prepared for operation with multiple blood transfusions.

At operation on May 18, 1949 an antral adenocarcinoma was found and a total gastrectomy performed. The duodenal stump was closed easily in 3 layers and buttressed to the pancreas. A rubber drain was placed at the operative site and brought out through a lateral stab wound.

Postoperatively, a duodenal fistula developed through the drain site on the fourth day and drained profusely. The patient died on the eleventh postoperative day of generalized peritonitis.

Autopsy disclosed necrosis of the duodenal stump at the suture line, and generalized peritonitis.

Obstructive factors. Four of the 13 cases of stump leakage in this series were associated with some form of obstruction distal to the stump. No unusual difficulty was encountered in obtaining closure of the stumps. Cases 10 and 11 were antral stumps and the remaining Cases 12 and 13 were duodenal stumps. In 3 of these cases, the ulcer was excluded at operation and in 1 it was removed. Obstruction probably occurred at the site of the excluded ulcer in 2 cases (Cases 10 and 12), in

the afferent loop in 1 case (Case 13), and at the stoma in 1 case (Case 11). Leakage occurred any time after operation up to 17 days, except in 1 late case (Case 13) which actually represents duodenal perforation occurring on the forty-first day after operation. Late perforation is typically due to afferent loop obstruction and has been reported to occur as late as 5½ months postoperatively.

In this group of 4 cases, 1 patient recovered and 3 died.

CASE 10. A 39 year old white male (BCH 925118) was admitted to the hospital January 2, 1939 with a history of stomach trouble of 15 years' duration. Episodes of pain, nausea, and vomiting had been present for 3 years. The most recent attack began 2 months prior to entry and resulted in a weight loss of 30 pounds.

Following medical treatment in the hospital, a gastrointestinal barium x-ray study was performed, disclosing an obstructing duodenal ulcer.

At operation on February 11, 1939, a markedly scarred anterior ulcer was found in the second portion of the duodenum, and a gastric resection with retrocolic Polya anastomosis was performed. Because of the marked inflammation and scarring surrounding the ulcer site in the duodenum, the stomach was transected proximal to the pylorus which was closed over as an end stump, leaving the ulcer in situ.

On the first postoperative day, the patient developed a left lower lobe pneumonia, due to type V pneumococcus. There was transient jaundice noted on the third day. The temperature spiked daily to 101 degrees F. during the first 2 weeks postoperatively. The pneumonia was treated with intravenous sulfanilamide. Fifteen days postoperatively wound infection occurred, followed 2 days later by sudden epigastric pain, rebound tenderness with absent bowel sounds, and high temperature. Leakage from the antral stump was suspected.

An emergency laparotomy was performed on the seventeenth postoperative day, disclosing yellow ascitic fluid in the peritoneal cavity. The cause of the peritonitis could not be found at operation. The abdomen was therefore closed, and the patient returned to the ward. He succumbed 2 days later.

Autopsy disclosed a disrupted antral stump with a left subdiaphragmatic abscess and generalized peritonitis.

CASE 11. A 56 year old white male (BCH 1325444) was admitted to the hospital on June 14, 1949, with a complaint of having collapsed following passage of a tarry stool 1 day prior to admission. He had a 26 year history of duodenal ulcer.

For 1 month prior to admission epigastric pain had increased and nausea and vomiting were severe. The patient could take only liquids by mouth and had lost about 30 pounds.

In the hospital, x-ray studies and esophagoscopy revealed a duodenal ulcer and esophagitis. He was given medical treatment including several transfusions of whole blood with fair response.

At operation on July 14, 1949 a posterior ulcer in the first portion of the duodenum was found. In order to obtain an adequate cuff for closure, a small portion of the pyloric antrum was turned in and the ulcer was excluded. A subtotal gastrectomy with antecolic Hofmeister anastomosis was performed.

The postoperative course was complicated by a nonfunctioning stoma requiring constant gastric suction for 8 days. The aspirated fluid did not contain bile. On the eighth day there was a sudden onset of epigastric pain accompanied by vomiting. The abdomen was spastic and tender with decreased peristalsis. The patient recovered from this episode, but on the twenty-fifth postoperative day a fistula developed in the wound and began draining duodenal contents. The duodenal fistula closed spontaneously 16 days later with conservative therapy.

CASE 12. A 57 year old white female (BCH 1048440) was admitted to the hospital December 1, 1941, with a chief complaint of epigastric pain and vomiting for 1 week. She had had ulcer symptoms intermittently during the previous 5 years. Gastrointestinal x-ray examination 1 year prior to entry revealed a duodenal ulcer with 30 per cent retention of barium after 6 hours. Six months prior to entry she passed a tarry stool.

Operation on December 4, 1941 revealed a penetrating, scarred, posterior ulcer in the second portion of the duodenum. The ulcer was excluded, the duodenal stump closed, and a subtotal gastrectomy with antecolic Hofmeister anastomosis performed.

Postoperatively, the patient developed severe epigastric pain on the second day and went into shock. During the next several days she developed a temperature up to 104 degrees F. The abdomen remained distended and silent. The diagnosis of peritonitis was made and the patient was treated intensively with chemotherapy, constant suction, and supportive measures. The diagnosis of leaking stump was not made before death on the seventh postoperative day.

Autopsy revealed a leak between the sutures of the duodenal stump with generalized peritonitis and with constriction of the duodenal lumen at the site of the excluded ulcer which had penetrated into substance of the pancreas.

CASE 13. A 37 year old white male (BCH 1231897) was admitted to the hospital on October 7, 1946, complaining of epigastric pain and vomiting of 6 months' duration. Six years previously he had been hospitalized for similar complaints. Four months prior to entry his food intake diminished because of vomiting after ingestion. During this period there was a weight loss of 42 pounds.

In the hospital the patient was placed on measured intake and output and found to have a complete obstruction. Barium x-ray studies showed a scarred, obstructing duodenal lesion.

At operation on November 1, 1946, a scarred anterior ulcer was found in the second portion of the duodenum. A subtotal gastrectomy with antecolic Hofmeister anastomosis was performed, the ulcer removed, and the duodenal stump closed without difficulty.

The patient made an uneventful recovery and was discharged in 2 weeks.

On December 12, 1946, the patient was readmitted several hours after the sudden onset of generalized abdominal pain of moderate intensity. Although the white blood cell count was 26,000, the temperature was normal. The abdomen was moderately tender throughout, particularly in the right lower quadrant. A urinary diastase determination was normal. The patient was thought to have a stomal ulcer and was placed on a medical regimen. He failed to improve and during the second hospital night he awoke in a profuse sweat and expired suddenly.

Autopsy revealed a generalized peritonitis with a pinpoint perforation in the duodenal stump 3 centimeters distal to the suture line. The afferent jejunal loop was obstructed by a mesenteric band 5 centimeters proximal to the gastrojejunal anastomosis, around which it had twisted.

DIAGNOSIS AND TREATMENT

Early recognition of stump leakage is essential to a lowering of mortality following gastric surgery. The diagnosis will be made only if thought of, and should be suspected when upper abdominal pain and spasm develop during the postoperative period, particularly when associated with an elevation in temperature of 101 degrees F. (oral) or higher. This degree of temperature elevation was found in all but 1 case (Case 13) reported in this series, whether or not antibiotics were used. A sharp rise in pulse accompanies the temperature elevation.

The frequency with which pulmonary complications in the lower lobes accompany this syndrome should be recognized. Conversely, thorough examination of the abdomen is mandatory when pneumonitis in the lower lobes develops postoperatively. In this series, 6 of 13 patients developed trouble above the diaphragm, 5 left sided and 1 on the right. This association has not been much affected by the antibiotic era since 2 cases occurred in 1950 and had the benefit of these drugs.

It is obvious that the clinical picture may in some cases become quite confusing since the escaping duodenal fluid may remain temporarily localized for a time and then spread to any quadrant of the abdomen, creating a changing abdominal picture in its wake. In addition, the patient may be having a degree of abdominal discomfort and pain due to the operation and may even be under the effects of narcotics and sedatives to confuse the symptoms further.

A common sequence of events is the development of a subdiaphragmatic or subhepatic abscess which, after surgical drainage, results in a fistula which digests the tissues of the abdominal wall. Sometimes a fistula develops spontaneously through the operative wound and is mistaken for wound infection until digestion of the tissues betrays its presence.

Once the diagnosis is made with reasonable certainty, early incision and drainage of the area of the disrupted stump offer the best chance for survival. In the present series, only 1 patient had early operation and drainage on the day after leakage occurred (Case 7). Unfortunately, this patient succumbed to a left pulmonary empyema 2 days later. Larsen and Foreman report only 2 of 15 patients with this syndrome whose symptoms were correctly diagnosed early and who were operated on for the express purpose of relieving this complication. Both patients survived whereas, of the remaining 13, some of whom had late drainage of obvious abscesses, only 2 survived. In our series, there were only 3 survivals, 2 following late surgical drainage, and 1 following development of a spontaneous fistula.

The development of a fistula, whether spontaneous or surgically produced, should be looked upon as the first stage in the successful management of stump leakage. Once a fistula becomes established the conservative regimen of sump pump suction of the drainage, skin protection with various substrate pastes, and acidifying agents combined with careful electrolyte and fluid balance control should be instituted. Many fistulas will respond well to this treatment.

Lest the condition of the patient declines under this conservative therapy, close watch of the blood electrolytes should be kept, since profound changes may occur within 24 to 48 hours. In such instance, emergency feeding jejunostomy should be performed before the

patient is allowed to deteriorate too far, and replacement therapy begun. Should it become necessary to perform a feeding jejunostomy, then a second jejunostomy tube should be inserted proximally and guided upward into the duodenal stump. The duodenal contents may then be aspirated through this proximal tube and fed back into the distal feeding jejunostomy tube. This double jejunostomy was carried out with remarkable success in a case followed by one of the authors at another hospital and is to be reported later.

PREVENTION

Much has been written concerning techniques of duodenal stump closure in which the ulcer is exteriorized and the suture lines are made to include or overlie the ulcer. Nevertheless, the dangers inherent in utilizing abnormal tissues in the duodenal closure should be obvious. Cases 1 through 4 in which these techniques of duodenal closure were used, all developed leakage within 72 hours of operation with 1 possible exception (Case 3), emphasizing the very tenuous nature of the closure.

In those cases in which systemic factors inimical to healing are present, adequate steps for their correction should be taken, prior to operation, if at all possible. It is recognized that there will be those cases of malignancy, bleeding, or associated disease in which operation must be carried out in the presence of varying degree of visceral depletion. In this series disruption from this cause was found to occur later than when local factors predominate; on or after the fourth day in all 3 cases. It is interesting that in none of the 3 cases presented in this group did leakage occur at the gastroenterostomy anastomosis, although it was subjected to the same deficiencies which affected healing of the duodenal stump. This observation is further borne out by the apparent rarity of reported leakage from the gastroenterostomy stoma. The explanation obviously lies in the fact that the duodenal stump is subjected to far greater physiologic stresses than the stomal anastomosis.

Obstruction has long been considered one of the most important factors in the pathogenesis of duodenal stump dehiscence. As a contributory cause of duodenal stump leakage it is most commonly seen occurring in the afferent loop, due to torsion or kinking of the loop, or at the site of a malfunctioning stoma. Occasionally it occurs in the efferent loop as in Case 6 in which the efferent loop became obstructed by the inflammatory process near the duodenal stump. When, for one reason or another, the stomach does not act as a decompressing reservoir for the obstruction, back pressure is transmitted into the afferent loop and into the duodenal stump. This sequence can be obviated by checking the stomach tube for patency at frequent intervals.

What has probably not received the recognition it deserves, however, is obstruction occurring at the site of an ulcer which has been left behind in the duodenum. If the preoperative history of the ulcer patient indicates that his ulcer has been obstructing in type, considerable caution should be used in electing to exclude such an ulcer at operation. Reactivation of an excluded ulcer in the duodenal stump has been conclusively demonstrated by the x-ray technique of Lorber and Shay. In Cases 10 and 12 dehiscence of the stump probably occurred as a direct result of obstruction at the site of the excluded ulcer. Both cases had a history of obstruction preoperatively, and in both it was elected to exclude the ulcer at operation because it was not feasible to remove it. In neither of the cases could local or systemic factors of any significance be indicted as contributing to the result.

Since subtotal gastric resection has become a fairly well standardized operation in recent years, it is being performed more and more by surgeons with varying degrees of training. A brief historical review of some of the procedures designed to obviate stump leakage would therefore be in order at this point.

Various surgeons have devised a number of ingenious procedures from time to time with the purpose of preventing a stump blowout. Kelling, in 1923, believing that disruption of the stump was in part due to damming back of duodenal secretions into the blind loop, practiced the use of an enterostomy between the afferent and efferent loops of the gastrojejunostomy, unaware at the time of the potential

danger of sidetracking alkaline duodenal secretions from the stoma. In spite of this potential danger Nissen uses this procedure frequently and reports no increase in the incidence of stomal ulcer. Lewitt attempted to relieve the build-up of pressure in the blind loop by suturing the open end of the duodenal stump to an adjoining loop of jejunum (end-to-side anastomosis). The procedure never gained acceptance since it prolonged an already lengthy operation.

St. John, Harvey, Gius, and Goodman and Colp employed a rubber drain placed near the duodenal stump to provide an avenue of exit in the event of duodenal leakage. It is interesting to note that even the use of a prophylactic drain at the duodenal stump may fail to prevent the development of generalized peritonitis in the event of leakage; e.g. Cases 4, 6, and 9.

The two stage procedure of McKittrick, Moore, and Warren, initiated in 1944, offered a different approach. A sleeve resection of the stomach with gastroenterostomy and exclusion of the gastric antrum (and duodenal ulcer) are performed in the first stage. The antrum and ulcer are dealt with 6 weeks later at a second stage when they can be more easily removed.

More recently, Welch reported the use of catheter duodenostomy in those cases in which it is not possible to obtain safe duodenal closure. A small cuff of duodenum is freed up and closed around a catheter which is brought out through a separate stab wound incision in the right upper abdomen. The catheter is placed on suction postoperatively, and the aspirated duodenal contents are returned to the gastrointestinal tract via a feeding jejunostomy tube placed at the time of operation. The duodenal catheter is removed in 10 to 12 days and the small resulting duodenal fistula is reported to close rapidly. This method of dealing with these difficult ulcers would seem to be preferred over the two stage McKittrick operation, if the ulcer is obstructive in type.

Lahey and Nissen, long time advocates of ulcer removal, in recent reports suggest their preference for vagectomy with gastroenterostomy rather than subtotal gastric resection in these very difficult cases. This attitude is strengthened by the comparative figures reported by the Vagotomy Committee of the American Gastroenterological Society reviewing the results of the two operations (11, 14).

The Billroth I technique avoids the duodenal stump, to be sure, but requires a normal duodenal cuff for anastomosis and therefore cannot be used in the presence of marked scarring or inflammation. It is worth while recalling that, with an anastomosis leak in the Billroth I procedure or any other procedure that re-establishes gastroduodenal continuity, even the successful establishment of a lateral duodenal fistula will carry a prohibitive mortality.

Another procedure which seeks to avoid the duodenal stump is Wangensteen's segmental gastric resection combined with pyloroplasty, performed through a sternum splitting incision. This operation has been recommended for all duodenal ulcers and particularly for scarred posterior penetrating ulcers. This technique, however, requires a longitudinal incision through the pylorus and anterior duodenal wall which is then closed transversely, an undertaking which would be contraindicated in the presence of an inflammatory reaction in these tissues.

SUMMARY AND CONCLUSIONS

1. An analysis of 13 proved cases of duodenal or antral stump leakage complicating gastric resection is presented.

2. An attempt is made to separate the causes of stump leakage in each case into three categories based on systemic, local, and obstructive factors for the purpose of gaining a clearer understanding of the pathogenesis of this complication.

3. Early diagnosis and surgical drainage are prerequisites to lowering the mortality of this complication.

4. A brief discussion and historical review of methods of preventing the complication are presented.

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A BACTERIOLOGIC AND CLINICAL STUDY OF BREAST ABSCESS

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THE purpose of the present article is to present a clinical and bacteriologic review of breast abscess for the period ranging from 1948 to 1953. This disease is a plaguing one for the obstetric service in any hospital and may assume epidemic proportions in a particular institution. Unfortunately, it is a more plaguing disease to the mother and sometimes may result in a prolonged hospital stay, a disfigured breast, and a complete disruption of her family. Many interesting changes have been made possible in the treatment of mammary infection with the advent of the new antibacterial drugs. Penicillin was, in the early part of this study, the drug of choice; but as we carefully followed the progress of the cases, it became apparent that the particular Staphylococcus aureus which caused puerperal mastitis was consistently resistant to penicillin and had characteristics of a specific strain.

ETIOLOGY

As to the etiology of the disease, many theories have been advanced; for example, let-down reflex and lactation failure, fissured and cracked nipples, or other types of trauma to the breast. The mode of entrance of this organism into the breast has never been proved. However, many studies reported within the past 10 years definitely prove that the organism is generally harbored in the nose and throat of personnel caring for the patient and the baby. The baby may be the carrier of this staphylococcus and transmit it to the mothers' breast. There are instances in this series in which both the baby and mother had similar breast abscesses and the same organism was recovered. Reports show the necessity, during an epidemic, of quickly culturing the nose and throats of hospital personnel and checking this same personnel for skin infections, such as pyodermia.

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BACTERIOLOGIC STUDY

During the past few years since penicillin therapy has played such an important part in the treatment of staphylococcus infections, it has been observed by the authors that strains isolated from breast abscesses were quite consistently resistant when tested in vitro against the antibiotic and likewise many cases proved refractive clinically to penicillin therapy. During the past 5 years, strains of Staphylococcus aureus have been isolated from 131 breast abscesses as compared to 494 strains from sources such as other soft tissue abscesses, wound infections, osteomyelitis, and blood cultures or such skin-borne infections. All strains of upper respiratory tract, urine, and exudate origin are excluded from this report.

Among the early breast cases studied from 1948 to 1950 staphylococci isolated from 3 cases showed resistance to 1 unit of penicillin per milliliter of media, while another resisted 2 units. Since, with this method, sensitive organisms were considered inhibited by 0.0625 unit or less, it became apparent that highly resistant strains were being encountered. There seemed to be no typical yearly distribution, the increase in number of breast abscesses not corresponding with the increase of general staphylococcus infections, a high incidence appearing in 1950 when the lowest number of general infections was encountered.

ANTIBIOTIC SENSITIVITY

Beginning with 1950, a comparative study was commenced to show the effectiveness of 3 antibiotics known to be specific against Staphylococcus aureus; namely, penicillin, streptomycin, and aureomycin. The results of a study of their effectiveness against strains isolated from breast abscesses as compared

with strains from other sources, as mentioned before, are reported in Table I.

All strains studied were isolated in pure culture from the site of infection. All strains included in this report were staphylococci, variety aureus, hitherto referred to as Staphylococcus aureus, which produced hemolysis on blood agar, were all coagulase positive, and gave similar biochemical reactions with 5 sugars tested. The plate dilution method was used.

From results of tests made on the first 7 strains of Staphylococcus aureus isolated from breast abscesses it was noted that only 1 strain was sensitive to penicillin, inhibited by 0.1 unit of the drug. On the other hand, 2 strains required 100.0 units, 1 strain 10.0 units, and 3 strains 1.6 units for complete inhibition of growth. The average coefficient of resistance[1] to penicillin of this group was 609.0, while that to streptomycin was 1.4, and to aureomycin, 4.0.

From a similar study made simultaneously with these antibiotics, but on strains of Staphylococcus aureus isolated from 16 patients with infections from miscellaneous sources, it was found that the average coefficient of resistance to penicillin was 135.0. This high figure was created chiefly by 2 very resistant strains, 1 showing a coefficient of resistance of 2,000.0 and 1 of 100.0. It is interesting to note that both groups responded to streptomycin in the same manner with a coefficient of resistance of 1.4, while that to aureomycin was 3.0, slightly less than the first group containing all strains from breast abscesses. Since our series of breast cases tested was small, the study was continued until a total of 26 strains had been isolated, tested, and compared with a like number of strains cultured from miscellaneous sources. Although with a larger series of breast abscesses the average coefficient of resistance was 276.0, it was still 38.0 per cent higher than that of the miscellaneous group with a coefficient of resistance of 105.0. The results with streptomycin and aureomycin were approximately the same. Of this entire series, only 1 breast abscess strain proved to be as sensitive as the control Smith strain, while 9 strains from the miscellaneous group were as sensitive as the control organism.

[1] Coefficient of resistance = Sensitivity of unknown organism or test organism / Sensitivity of control organism, the sensitive Smith strain

TABLE I.—COMPARATIVE EFFECT OF 3 ANTIBIOTICS ON STRAINS OF STAPHYLOCOCCUS AUREUS ISOLATED FROM INFECTIONS

Antibiotic	Average coefficient of resistance*	
	Breast abscesses, 26 cases	Miscellaneous infections, 26 cases
Penicillin	275.76	105.36
Streptomycin	2.03	2.23
Aureomycin	4.42	2.07

*Coefficient of resistance = Sensitivity of unknown organism / Sensitivity of control organism

DIFFERENTIATION BY PHAGE TYPING

These findings suggested that we were dealing with different strains of staphylococci, even though they were all coagulase positive, hemolytic on blood agar, and gave similar biochemical reactions. Since it has been pointed out by Blair (2) that "staphylococcal phages of lysogenic origin are quite specific in their action," it was thought that an explanation of our findings might be found if the phage type of the various strains was studied. Bacteriophage is a filtrable virus, parasitic on bacterial cells, its presence manifest by the specific lysis of these organisms. Sensitivity to bacteriophage has proved an aid in the differentiation of individual strains of several bacterial spe-

TABLE II.—COMPARATIVE EFFECT OF 6 ANTIBIOTICS ON STRAINS OF STAPHYLOCOCCUS AUREUS ISOLATED FROM INFECTIONS

Antibiotic used	Of breast origin (24)				Of miscellaneous origin (24)			
	Resistant		Sensitive		Resistant		Sensitive	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Penicillin	21	87	3	13	16	67	8	33
Dihydrostreptomycin	8	33	16	67	10	42	14	58
Aureomycin			24	100	3	12	21	88
Terramycin			24	100	4	17	20	83
Chloromycetin			24	100	2	9	22	91
Bacitracin			24	100	1	4	28	96

TABLE III.—BACTERIOPHAGE TYPE OF STAPHYLOCOCCUS AUREUS ISOLATED FROM INFECTIONS

Phage type	Of breast origin (24)		Of miscellaneous origin (24)	
	Penicillin resistant	Penicillin sensitive	Penicillin resistant	Penicillin sensitive
I				4
II			2	
III(52a)	16	2	10	2
IV			1	
V				1
Not lysed	5	1	3	1

cies and has been used in recent years in studies on the staphylococci. Evidence has been presented to show that about 60 per cent of strains of Staphylococcus aureus can be grouped according to their sensitivity to a series of phages, and at the present time 6 phage types of Staphylococcus aureus are recognized by Blair and co-workers (3). Through the courtesy of Dr. Blair, at the Hospital for Joint Diseases in New York, the bacteriophage type was determined on the next series of strains isolated. At the same time, the more simple disk method was adopted for determining the antibiotic sensitivity and 3 more antibiotics included; namely, terramycin, chloromycetin, and bacitracin, while dihydrostreptomycin was substituted for streptomycin.

As is shown in Table II, of the 21 additional penicillin resistant breast abscess strains tested, all proved to be sensitive to terramycin, aureomycin, chloromycetin, and bacitracin. Eight of the strains were resistant to dihydrostreptomycin. At this time, 3 penicillin sensitive breast abscess strains were encountered and they were also sensitive to the 4 other antibiotics tested.

As is shown in Table III, the 21 penicillin resistant strains were phage typed and 16 proved to be type III, specifically subtype 52a, while 5 were not typed by any available phage. Of the 3 penicillin sensitive strains typed, 2 were subtype 52a and 1 not lysed. Confirmed by phage typing, all of the strains of Staphylococcus aureus from breast abscesses demonstrated a close homogeneous relationship.

During this same period, 16 penicillin resistant strains, isolated from miscellaneous infections, were phage typed. Ten proved to be type III, 52a specifically; while the remaining 6 strains were either not lysed or were types II and IV. Eight penicillin sensitive strains of the miscellaneous group also showed a variety of phage types as well as more variable reactions with the antibiotics tested. Phage typing showed this miscellaneous group to be a much more heterogeneous one than that of breast abscess strains.

The presence of penicillin resistant staphylococci in these breast cases seemed to be consistent regardless of age or sex, since 3 strains were from small children, 2 of whom were males, and 1 strain was from an adult male. Barber and co-workers have reported the incidence of penicillin resistance of Staphylococcus aureus isolated from infants, mothers, and hospital staff in general, a high percentage of which were type 52a. Spink has called attention to the alarming rate at which penicillin resistant strains are appearing in staphylococcus infections. Since our observation of breast abscess strains began in 1948, it has been evident that they have always been penicillin resistant to a higher degree than those strains from miscellaneous sources. It would seem very significant that of 24 strains typed thus far, 18 have proved to be type III, specifically 52a, the remaining 6 strains not lysed. On the other hand, of 24 miscellaneous strains typed, only 12 were type III, 52a, the remainder falling into other types or not lysed. There also appeared to be a definite relationship between the phage type of the breast abscess strains and their reaction with 4 of the other antibiotics, for both 52a and not lysed strains were sensitive to terramycin, aureomycin, chloromycetin, and bacitracin. There were more variable findings with the miscellaneous strains, as one would anticipate from the variety of phage types in this group.

TREATMENT

The treatment of puerperal mastitis is prophylactic, symptomatic, and surgical. Our experience, in these 131 cultured cases, shows that although penicillin is the recommended

treatment of choice, this drug is ineffectual, unless given in tremendous doses. It has a tendency, when given in such doses, to localize the abscess and attenuate the signs and symptoms. In 2 instances in this series, a thick-walled abscess cavity was formed which was not absorbed. In the end, it was necessary to remove this thick-walled abscess because it had all the characteristics of carcinoma. Breast abscess does occur in women who are not postpartum and there have been 2 such instances in this series.

The drugs of choice, at the present time, in the prophylactic treatment are streptomycin, chloromycetin, terramycin, and aureomycin, the latter two being preferable. At the first sign of inflammation, usually observed by the obstetrician, the chosen drug should be administered in quantities of 250 to 500 milligrams 4 times a day and this should abort the abscess. Aureomycin causes pruritus and vaginitis in some instances.

The symptomatic treatment is equivocal. There are those who believe that hot fomentations or cold fomentations of one sort or another are helpful in either inhibiting the progress of the inflammation or encouraging it to localize. Also the continuance of the baby's nursing on the affected breast or the discontinuance of the baby's nursing actually seems to have no proved worth to either mother or baby. The question of the use of hormonal drugs to stop lactation, such as stilbestrol, would seem to be a wise move to prevent engorgement. However, there are instances in which lactation has subsided and the breast abscesses have formed and gone on to suppuration. Adequate support of the breast is about all that is necessary. The mother and baby are best left to themselves. Since the advent of this type of treatment, a very sharp and quick decline in the number of infections of the breast which come to surgery has been noticed. There are just as many potential breast abscesses, but most of them are cured by antibacterial therapy. In 1950 there were 35 breast abscesses which we documented, and in 1953 there were 3.

If it appears that the breast abscess is not responding and is going on to suppuration, the patient should be immediately hospitalized. When the infection fails to show response to antibacterial therapy and there is definite localization, not necessarily with evidence of suppuration, the area should be incised and drained in a particular way. The breast being a compartmented structure, the first evidence of the beginning of suppuration is the pointing of the inflammation in the area about the areola. It was the practice some years ago to allow these breasts to go on to obvious clinical suppuration, at which time it was necessary to make a large radial incision over the suppurating area and break down the various compartment walls in order to obtain free drainage. This not only gave a disfiguring scar but many times permitted the entrance of secondary invaders such as Pseudomonas aeruginosa and helped to prolong the infection. The incision should be made around the areola of the nipple, through the skin and subcutaneous tissue, but not entering into the ducts. Then by careful, blunt dissection, preferably with a hemostat, the compartment of the breast involved is entered. Pus is almost uniformly encountered and by palpation of the breast, if another compartment is involved, the hemostat can be pushed into this compartment and the pus evacuated. This method does away with the long disfiguring radial incision and the possibility of secondary infection. The antibacterial drugs are continued during the surgical treatment.

When terramycin or aureomycin are used early and vigorously, the most severe infections can be completely aborted. However, if the administration is not begun until the infection is firmly established, unaided resolution is unlikely.

SUMMARY AND CONCLUSIONS

1. As a result of the study of Staphylococcus aureus isolated from 50 breast abscesses, it appears evident that these strains are penicillin resistant to a high degree, since only 4 sensitive strains were noted in the series.

2. Since these strains proved to be either phage type III, 52a, or not lysed, our findings suggest that breast abscesses are most often due to this strain and this strain only.

3. Sensitivity tests indicate that penicillin therapy is of little or no value, while terramy-

cin, aureomycin, chloromycetin, or bacitracin should prove of value in treating this apparently homogeneous group of organisms, as confirmed by phage typing.

4. Many more heterogeneous strains were encountered in the miscellaneous group of infections as shown by antibiotic reactions and phage type.

5. Breast abscesses going on to suppuration should be treated in the manner described.

6. The incidence of breast abscesses has decreased during the past 5 years.

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EDITORIALS

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SEPTEMBER, 1954

PREPARATION OF THE PATIENT FOR INTESTINAL SURGERY

OPERATIONS on the intestine have always been considered in the field of so-called major surgery. Before the days of aseptic technique, mortality associated with such operations was prohibitive. Even with the advent of greater knowledge about asepsis, peritonitis and its accompanying problems caused great loss of life when resections for carcinoma and inflammatory disease of the bowel were undertaken.

With increased knowledge of the nature of peritonitis and its associated symptoms, physicians and surgeons began to think of preventing this postoperative accident and to plan for its control. Although even today peritonitis still presents a major hazard for the surgeon performing intestinal resection, its incidence has been tremendously reduced by a variety of procedures. Among these are (1) active steps to combat the effects of the causative organisms, (2) preoperative cleansing of the bowel and changing the intestinal flora, and (3) greater attention to the maintenance of suitable fluid balance.

The organisms commonly present in the exudate found in the peritoneal cavity of a patient dying of peritonitis are streptococci and Escherichia coli. Extensive animal experimentations by Hermann, Poth, and others led to the belief that an individual could be protected from the development of peritonitis. This belief was based on the fact that when the peritoneal cavity of animals was soiled by spilling feces and then an intestinal resection was done, death from peritonitis was common. If, however, the animal had had an injection of a suitable mixture of killed streptococci and Escherichia coli into the peritoneal cavity several days prior to intestinal resection, with soiling, peritonitis almost never occurred.

As a result of these experiments, an antiperitonitis vaccine from similar organisms obtained from human beings was prepared and injected into the peritoneal cavity of men and women several days prior to the anticipated date of colonic resection. Subsequent to the adoption of this procedure, there was a striking reduction in the incidence of peritonitis after resection for carcinoma and other intestinal lesions. Whereas the mortality rate in the 1920's was around 15 to 20 per cent, after this and other measures of preoperative preparation were introduced the rate decreased to 5 and 6 per cent. Prior to this and during the time of such vaccination, other measures of preoperative preparation had been instituted. These included cleansing irrigation of the colon with saline solution twice daily, a suitable diet containing a minimum of residue, and small doses of saline laxa-

tives given periodically. However, the latter measures had been carried on for many years without much change in mortality figures.

With the advent of the sulfonamides, the antiperitonitis vaccine soon lost favor because similar or even better results could be produced by the administration of these drugs by mouth for several days before operations. Among the favored drugs in this group have been sulfasuxidine and sulfathalidine. With the advent of the antibiotics, even greater changes in the intestinal flora were produced so that practically all disease-producing bacteria of the intestinal tract could be destroyed by the administration of suitable amounts of the broad-spectrum antibiotics. Among those which have found particular favor are chlortetracycline (aureomycin), oxytetracycline (terramycin), neomycin, and erythromycin.

Intensive study and practical application of the principles of fluid balance in patients with intestinal disorders have taken place in recent years. At times the concentration of serum protein in these individuals was found to be considerably reduced. Its correction by blood transfusion and other appropriate measures seemed imperative before surgical resection was undertaken. In patients with long-standing intestinal disease, such as is seen in long-standing chronic ulcerative colitis, the serum potassium was frequently reduced to critical levels. The reduction has often been so marked that clinical and electrocardiographic evidence for such reduction was available. Its correction before operation is of the greatest importance. Then, too, reduction in sodium chloride and calcium has frequently been found, and the concentration of these elements should be brought up to normal or within normal range before surgical treatment is undertaken.

A program including the following measures of preoperative preparation has been found particularly efficacious for patients who are to have intestinal resection. Such a patient is given a minimal-residue diet, Fleet's phospho-soda twice daily, a combination of neomycin and oxytetracycline (terramycin), colonic irrigations with warm saline solution, paregoric the evening before operation, and aspiration with a rectal tube on the morning of operation. Attention to all these measures and careful selection of patients have made it possible to operate on large numbers of patients with major intestinal lesions during the last 5 years or more with a mortality rate of 2 to 4 per cent. This seems a rather remarkable achievement, and credit for this goes to the teamwork of the laboratory worker, the physician, and the surgeon. J. ARNOLD BARGEN.

THE SURGEON'S BIB

THERE are those of us who are old fashioned enough to believe that surgery is an exacting discipline, jealous lest its requirements and accomplishments be shared with or rendered less exacting by a commodity from the hospital pharmacy. Five hundred years ago Lanfranc demonstrated that union of two segments of intestine occurs between serosa and serosa. We now know that if two pieces of bowel are brought together, they agglutinate quickly and within a week's time carry out their normal responsibilities to the host provided that the blood supply to each end is undisturbed, the surfaces come together in an easy relaxed way, and apposition is maintained by carefully placed sutures which are only heavy enough to be securely tied.

There is no convincing evidence that healing occurs more promptly or more securely if the contents of the bowel are "sterile." Nor is it proved that antibiotics afford protection against disruption of a suture line from inade-

quate blood supply to a segment, or from tension, or from the careless approximation of surfaces.

As little children we all wore bibs. As we progressed in life and our techniques improved, we no longer needed the protection they provided. In fact, we resented it. We even learned that, with the possible exception of eating lobster in Atlantic City, a bib or even a napkin tucked in the collar was not necessary for either the safety or enjoyment of a full course meal.

When we attend the annual Congress of the College this fall we may be a little amused at the bib which is offered us at the lobster house. Then we find ourselves actually enjoying a certain relaxation in cracking the lobster claw and removing its tasty contents. We are really surprised to find that the waitress was right. The paper bib with the large lobster and the management's name in red letters is soiled and undoubtedly did protect our clothes. Then later, in the more restful atmosphere of Ye Olde Oyster House, we realize that here in Boston we have enjoyed our lobster with the same security as in Atlantic City and actually the slightly more careful technique we used was neither time-consuming nor difficult.

To those of us who, like Ambrose Paré, believe in the fundamental normalcy of the healing processes in man when tissues are tenderly handled and left so far as possible in their natural state, there is neither need nor justification for the surgeon routinely to divide the responsibility for an intestinal anastomosis between his surgical skill and the antibiotics. We may even wonder if the reaction, mild or fatal, which occasionally follows the use of these agents may not suggest resentment on the part of the body to their interference with a function which it is so well devised to carry out.

Has the time not arrived and is it not our obligation to encourage the young surgeon to discard his paper bib, to help him develop the proper technique, and to have the confidence in it which his newly acquired skill so richly deserves? Are we as leaders in surgery today and teachers of the surgeons of tomorrow keeping faith with our heritage and with these young men and women when we so readily accept questionable and certainly unnecessary aid from the antibiotics following the completion of routine surgical procedures which need only be done under proper conditions and with the care and skill to be expected of any who would be called a surgeon?

Could it even be that we are fostering a generation of surgeons with a false sense of values which is developing in an atmosphere inspiring confidence in and dependence on the injections given by a nurse, rather than enjoying the genuine pride and deep satisfaction which come from the skillful application of knowledge, experience, and imagination? These, after all, are the real attributes of the surgeon, to be carefully and continuously developed and deeply respected.

LELAND S. MCKITTRICK.

THE SURGEON AT WORK

THE ROUTINE USE OF ANTIBIOTICS IN ELECTIVE ABDOMINAL SURGERY

LELAND S. McKITTRICK, M.D., F.A.C.S., and FRANK C. WHEELOCK, JR., M.D., F.A.C.S.,
Brookline, Massachusetts

IN RECENT years we have noted a widening utilization of the antibiotic agents in preparation for, or following routine surgical procedures. We have questioned the necessity as well as the desirability of dividing the responsibility for an elective surgical operation on the gastrointestinal tract between the technique of the surgeon and the chemotherapeutic or antibiotic agents. The increasing number of serious, even fatal, complications following the use of the antibiotics would seem to place upon us the responsibility of presenting evidence that the benefits to our patients from their routine use clearly outweigh the hazards, and that the potential dangers against which they are supposed to protect cannot be avoided by careful surgical technique.

The importance of proper evaluation of these medicines was brought to our attention by a young colleague who had recently settled in a midwestern city. When discussing this problem with some of his friends, he was told that if he did not use antibiotics following an operation on the bowel he might be liable to a malpractice suit if the postoperative course of any of his patients was unsatisfactory.

It has been our policy to restrict the use of the antibiotics to those cases in which there were definite indications for their use. In general, patients with chronic bronchitis, rheumatic heart disease, abscess around a lesion of the bowel, and a very low anterior resection, where it is impossible completely to control bleeding and bowel contents during the anastomosis, were considered to be deserving of whatever protection penicillin and streptomycin might offer. Lest by not conforming to the local and widespread practice of the routine use of these agents following resection of the gastrointestinal tract we might be denying our patients protection which should be afforded them, we felt it our obligation to review a group of our own cases and compare their postoperative courses with those of a similar group of cases done by other members of the visiting staff.

The control group consisted of consecutive patients operated on by the visiting staff (in the Baker Memorial division of the Massachusetts General Hospital) from October 1952 through February 1953. Ours were also consecutive, unselected patients, but in order to obtain sufficient cases, of necessity the dates extend back over a longer period.

RESULTS

The records of 175 patients have been carefully reviewed with particular reference to: (1) age, (2) duration of hospital stay after operation, (3) presence or absence of infection in relation to the field of operation or abdominal wound, and (4) degree of fever during the postoperative course. Any patient with a temperature of 100 degrees F. after the fifth postoperative day is recorded as having had a febrile course. In addition to this we have recorded the highest temperature of each patient.

Subtotal gastrectomy. In 25 consecutive subtotal gastrectomies performed for ulcer and in 4 gastrectomies for cancer, antibiotics were used postoperatively in only 5. The reasons for using them were primarily because of existing chest signs or symptoms.

Thus 24 of our patients were given no antibiotics. The average age was 50 years, including 2 patients over 70. The average hospital stay was 12.5 days after operation, and the only complications were thrombophlebitis in 1, transient stomal obstruction which resolved itself in 1, and atelectasis in 2 (1 of whom was treated then with penicillin). No patient had a "febrile course" as defined previously. The average of the highest postoperative temperature was 100.6 degrees.

This group we compared with a group of 36 consecutive patients, operated on by other visiting surgeons at the Massachusetts General Hospital, who received antibiotics prophylactically. Patients over 70 were excluded from this group since over this age it might be argued that antibiotics

were indicated, and their use, therefore, therapeutic rather than prophylactic. The average age here was 54.6 years. The average postoperative stay was 15 days. Complications were atelectasis of moderate degree in 3, thrombophlebitis in 2, and mild wound infection in 1. Eight patients ran a febrile course, the cause of which was not apparent. The average of the highest temperature recorded was 101 degrees.

Biliary tract. No antibiotics were administered in a group of 33 patients with an average age of 55 years upon whom cholecystectomy was performed. The complications were wound abscess, glaucoma, fatal coronary occlusion, and thrombophlebitis. The average postoperative hospitalization was 10.7 days. The average highest postoperative temperature was 100.3 degrees.

Twenty-four patients were given antibiotics postoperatively for no reason other than "prophylactic." The average age was 54 years and the average postoperative stay was 12.3 days. One patient who had no pancreatitis at operation, died of acute pancreatitis on her fourth day. Another developed pancreatitis, 2 had wound infection, and another had trouble with atelectasis. Three had febrile courses and are included in the complication list. The average highest postoperative temperature was 100.5 degrees. (Twelve of this group and 10 of the no antibiotic group had common duct explorations.)

Resection of colon with anastomosis. In our past 42 consecutive colon resections exactly half[1] received no antibiotics. No patients operated on by others escaped antibiotics. The 21 patients who had no medicine of this type ranged in age from 39 to 86 years with an average age of 63.5. Eight were 70 or over and 2 of these over 80. The average postoperative stay was 13.4 days and the average highest fever 100.8 degrees. Five patients had a "febrile course." In 2 this was not explained and did not prolong hospitalization. One other had phlebitis and another slight transitory unexplained jaundice, and the last had mild pelvic cellulitis after a low anastomosis. The 86 year old patient died of myocardial infarct on her seventh day after operation.

The group who received prophylactic antibiotics averaged 62.8 years of age and stayed in the hospital an average of 15.2 days after operation. Their average highest temperature was 101.8 degrees. Six ran a "febrile" course. Two died, 1 of uremia of unknown cause and 1 of pulmonary infarction. One developed small bowel obstruction requiring surgical correction and another developed an abscess.

[1]The specific indications for antibiotics in those cases were low resection with anastomosis, abscess about the carcinoma, marked obesity complicating surgery, and pulmonary disease.

TABLE 1.—SUMMARY OF COMPARATIVE STUDY IN ELECTIVE ABDOMINAL OPERATIONS

	No antibiotics	Prophylactic antibiotics
No. of patients	78	82
Average age, years	55.6	56.6
Days in hospital postoperative (average)	12	14.3
Highest temperature postoperative (average all cases), degrees F.	100.5	101.1
Complications		
Infection	2	4
Atelectasis	2	4
Febrile course	5	14
Thrombophlebitis	2	2
Miscellaneous	3	2

The two groups correlated closely in the location of the tumors in the colon. Progress in the group not given postoperative antibiotics seems to have been as satisfactory as in the group given them. The group who received antibiotics for specific indications ran courses comparable to these two groups.

Closure of colostomy. Of 15 of our patients with colostomy closures only 1 received antibiotics. The other 14 ranged in age from 38 to 84 years and remained in the hospital an average of 9 days. None had a febrile course, and the only complication was mild wound infection in 1 case. This was discovered on the sixth postoperative day and the patient went home 2 days later. No control group seemed necessary in this group as such satisfactory postoperative progress was made in all cases.

SUMMARY AND CONCLUSION

A small group of patients of similar age and social and economic backgrounds who were operated upon by surgeons of comparable experience were carefully studied relative to the effect of the antibiotics upon the postoperative courses following certain elective operations. The group is much too small to have statistical significance but was intended as a pilot group, careful study of which might suggest the need for further investigation or at least afford some evidence for or against the prophylactic use of these agents.

One hundred and seventy-five patients with operations upon the gastrointestinal or biliary tracts were studied. This study failed to demonstrate benefits which are necessary to compensate for the discomforts, expense, and possible dangers associated with the prophylactic use of antibiotics following most elective operations on the gastrointestinal and biliary tracts.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

IN Germany and many other European countries, operations on the brain and the spinal cord are still performed by almost every capable general surgeon. Dr. Guleke is professor of surgery and director of the Department of Surgery at the University of Iena and is a pupil of another great surgeon who was one of the pioneers in neurologic surgery, Ernst von Bergmann. In general, the book *Die Eingriffe am Gehirnschaedel—Gehirn an der Wirbelsaeule und am Rueckenmark*[1] reflects the thoughts, methods, and the techniques which were employed by the great general surgeons before the advent of specialized neurosurgical techniques, and therefore will give the student, the physician, and surgeon an erroneous notion of neurologic surgery as it is practiced today. The more detailed descriptions of operations and the majority of the illustrations are devoted to procedures today abandoned by the specialist. Antiquated procedures are more fully described and illustrated and given greater importance than modern successful interventions; this applies especially to the chapters on the treatment of trigeminal neuralgia, brain abscess, sellar and parasellar tumors, and internal hydrocephalus. On the other hand, very little is said about the treatment of protruded intervertebral disc, arterial aneurysms, subdural hematomas, about lobotomy, arteriography, and other modern diagnostic procedures. Diagnostic brain puncture, as described in 1904 by Neisser and Pollack, which is described in detail, is today nearly completely abandoned. From a historic point of view this book is very valuable and makes us realize the importance of the contributions of Cushing, Dandy, Elsberg, Frazier, and others. It may also keep the young surgeon from discovering new methods of treatment which were used 40 and 50 years ago and which are not mentioned in our new textbooks on surgery. Paper, binding, printing, and illustrations are excellent. There is no bibliography.

GEORGE PERRET.

THE excellent publication on the surgery of the newborn and young infant[2] by Duhamel of the Hôpital des Enfants-Malades in Paris is an outstanding contribution and unquestionably ranks high in the French literature just as the recent book by Robert Gross on the surgery of infancy and childhood holds a pre-eminent place in this country. It is dedicated to the memory of Professeur Jacques Leveuf, and the preface is written by Professeur Marcel Fèvre under whose able direction much of the work at the Children's Surgical Clinic was done and from which the data for this publication were obtained.

This book is not intended to be a complete work on children's surgery and deals not at all with orthopedic surgery or other surgery of the extremities. Its object ostensibly is to emphasize clearly the necessity of using special methods of diagnosis and special methods of treatment when dealing with very young babies, and also the necessity for the closest co-operation and teamwork between the surgeon, the pediatrician, the anesthetist, and those responsible for the meticulous preoperative and postoperative care of these little patients if successful results are to be expected. It embraces three major fields: (1) the surgery of congenital malformations, especially those which are incompatible with life and therefore demand immediate surgical intervention, i.e., atresia of the esophagus and atresia of the duodenum; (2) surgical lesions which are peculiar to infancy, i.e., congenital pyloric stenosis and intussusception; (3) lesions common to all ages of life, but presenting peculiar characteristics when encountered in infancy, i.e., appendicitis and diaphragmatic hernia.

The chapter on anesthesia, upon which great stress is laid, was written by Michel Bourgeois-Gavardin; that on radiology, which plays a most important role in diagnosis in infancy, by Jacques Sauvegrain; and the one on otorhinolaryngology by Charles Autier. Otherwise this work is the product of Bernard Duhamel himself, and in the bibliographies which accompany each chapter one finds many references to his contributions to the literature.

If one were asked to compare this book with that of Robert Gross of Boston one might be justified in saying that it is less broad in its scope, it is based on a smaller volume of clinical material, the photographs and other illustrations are far less numerous and not quite as clear cut, the discussion by the author on the relative merits of the various surgical procedures is much less complete, and the follow-up studies on the operated cases are not as thoroughly carried out.

[1] ALLGEMEINE UND SPEZIELLE CHIRURGISCHE OPERATIONSLEHRE. Vol. 2, 2nd ed. By Martin Kirschner. Edited by N. Guleke and R. Zenker. DIE EINGRIFFE AM GEHIRNSCHAEDEL—GEHIRN AN DER WIRBELSAEULE UND AM RUECKENMARK. By Dr. N. Guleke. 2nd ed. Berlin, Goettingen, Heidelberg: Springer-Verlag, 1950.

[2] CHIRURGIE DU NOUVEAU-NÉ ET DU NOURRISSON. By Bernard Duhamel. Preface by Marcel Fèvre. 308 pages, 158 illustrations. Paris: Masson & Cie, 1953.

Nevertheless, it is a very interesting and very well written book, and is full of useful information for anyone concerned with surgery as applied to the newborn infant or very young baby.

EDWIN M. MILLER.

THE book entitled *Modern Trends in Urology*,[1] can be placed in the category of an outstanding text. It is well written and edited, and it reflects the dynamic and stimulating quality of the practice of urology in the British Isles. Every urologist and surgeon interested in this specialty should have this text on his bookshelf as he will find it of inestimable help in his practice. Its value as a teaching text indicates that it should be in the libraries of our hospitals and medical schools.

The reader, before he has perused one quarter of the book's 476 pages, will appreciate that the subject material has been carefully selected and grouped. This factor permits continuity of thought and ease of scientific appraisal and the appreciation of the value of one technique versus another.

The title of the book refers to modern trends; its scope is therefore limited and all the more decisive since it is not an all inclusive text. Thirty-seven authors have contributed to thirty-eight chapters which embrace the newer diagnostic modalities and which enunciate sound principles in the pathology, diagnosis, and therapeusis of infections, neoplasms, calculi, and the obstructive uropathy. The exposition of surgical technique in the management of certain diseases of the kidney, bladder, prostate, and urethra is covered in detail. Two highly interesting chapters deal with the investigative work of renal transplants and carcinogenic agents.

Chapters 1 through 5 discuss the relationship of urology to general surgery, the training of the urologist, the urologist's armamentarium, advances in the radiology of the urinary tract, and the contribution of the pathologist to urology.

Chapters 6 and 32 discuss the treatment of urinary infections (excluding tuberculosis) and genitourinary tuberculosis. Chapter 7 discusses anesthesia in urologic surgery.

Chapters 8 through 11 discuss the operative approach to the kidney, partial nephrectomy, and hydronephrosis and hydrocalycosis, renal denervation.

Chapters 12, 13, and 14 discuss the pathology of renal tumors, renal and ureteric neoplasms in the adult, renal neoplasms in childhood.

Chapters 15 through 18 cover the problems of renal transplantation, the treatment of uremia, transplantation of the ureters: indications and methods, and results and effects.

Chapters 19, 20, and 21 present a most worthwhile therapeutic symposium on surgical approach to the pathology of bladder tumors, surgical treatment of malignant growths of the bladder, and the radiologic treatment of growths of the bladder.

Chapters 22 through 30 give an excellent and complete coverage of prostatic disease and its pathologic physiology. The details of surgical technique are well described and illustrated. The chapters in order are as follows: "Indications for Treatment in Prostatic Obstruction," "Complications of Prostatic Obstruction," "Harris Prostatectomy," "Retropubic Prostatectomy," "Wilson Hey Prostatectomy," "Perineal Prostatectomy," "Transurethral Prostatectomy: the Punch Operation," "Transurethral Prostatectomy: Endoscopic Resection," and "The Malignant Prostate."

Chapter 31 discusses reconstruction of the male urethra in strictures.

Chapters 33 and 35 discuss the etiology and prevention of urinary calculi and the treatment of ureteric calculi.

Chapters 34, 36, 37, and 38 present the effects of carcinogenic agents in the urinary tract, the care of the urinary tract in paraplegia, injuries of the urinary tract in peace and war, and the urologic aspects of gynecology.

CHARLES A. W. UHLE.

THE book entitled *Sympathikus Chirurgie*[2] was written by Dr. Paul Sunder-Plassmann, director of the Surgical Clinic and Polyclinic of the University of Muenster in Westphalia, and professor in that institution. The monograph is written in German. It has 162 pages and 145 illustrations, many of which are diagrammatic sketches of histologic observations.

In the first 82 pages, the author presents his rather unorthodox view of the histologic and pathophysiologic aspects of the autonomic nervous system. His views are based on 4 main tenets: (1) He predicates the existence of a peripheral "neuroreticulum" as opposed to the more generally held view which recognizes the existence of discrete nerve endings. (2) He describes distinct cells, said to be related to mesenchymal cells, which he finds associated with the "neuroreticulum" which he proposes, and these cells are supposed to have a secretory function and to constitute, together with the "neuroreticulum," the "neurohormonal" system. (3) This "neurohormonal" system is capable of a certain autonomous function, even when separated from ganglion cells. (4) He does not accept the usual concept of synapses; instead he deduces, from histologic studies, that there is a plasmotic continuity, the "Nebenzellplasmodium," between the nerve endings. He hypothecates that this "Nebenzellplasmodium" is responsible for the production of local chemical substances important in nerve conduction, such as acetylcholine.

The remainder of the book is devoted to a discussion of surgery of the sympathetic system. Be-

[1] MODERN TRENDS IN UROLOGY. Edited by E. W. Riches, M.C., M.S., F.R.S.C. With a foreword by the Lord Webb-Johnson, K.C.V.P., C.B.E., D.S.O., T.D., M.B., LL.D., F.R.C.S. 476 pages, 215 illustrations. $12.50. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1953.

[2] SYMPATHIKUS CHIRURGIE. By Prof. Dr. Paul Sunder-Plassmann. 162 pages, 145 illustrations. DM 54. Stuttgart: Georg Thieme, 1953.

sides the usual, generally accepted conditions for which this type of surgery is employed, the author devotes some space to conditions such as megacolon, megaloureter, and other anomalies. However, he does not critically evaluate the indications for, and the results of, surgical treatment in these conditions. His interesting book would have been considerably improved had he included such evaluation.

HENDRIK J. SVIEN.

TWO main divisions, radiation treatment of benign diseases in part one and radiation treatment of malignant diseases in part two, compromise the volume entitled, *Gynaekologische Strahlentherapie; Indikationsstellung, Methodik und aerztliche Betreuung.*[1] There is a short section devoted to a general view of radiation therapy in the future.

In each of the two main divisions, the entire gamut of gynecologic disease is presented. In each instance indications for radiation therapy are given, and every type of technique is described and appropriate illustrations are used. Prophylaxis against and therapy of complications of radiation are given. Discussions are detailed and comprehensive, since the author presents the views and methods of other clinics if there is any variation from treatment as done in his own. Thus, in discussion of radiation treatment of carcinoma of the cervix, the methods as used at the Radium-hemmet in Stockholm, The Curie Foundation in Paris, and several clinics in Germany are given.

It is quite possible that therapists in this country will not agree with indications for radiation therapy as given for each disease, particularly if benign, but for gynecologist and radiologist alike the extensive presentation of radiation methods in this monograph is worthwhile and should be read.

FRANK M. MAHER.

THE book entitled *Diseases of Women*[2] represents the collective efforts of ten contributors selected from leading English authorities in gynecology. The present volume is the ninth edition since the first publication in 1919, attesting to the editors' and contributors' success in providing dogma and orthodoxy for students and young practitioners.

There are 43 chapters which range from the basic subjects of embryology, anatomy, physiology of hormones, and the menstrual cycle to individual disease entities, differential diagnosis and discussion of symptomatology, and operative procedures. There are 176 illustrations, done as drawings with the exception of a few of the histology representations. The latter usually are too low in magnification to show detail.

Of necessity in a book of 480 small pages, this wide range of subjects could not be presented in detail in most instances. The volume serves well as a representative survey of English thought in clinical gynecology rather than as a reference source. The many instances of similarity between concepts in this book and those in standard American texts as well as the interesting occasional differences of opinion should occasion as wide an interest among students and practitioners in this country as in England.

FRANK M. MAHER.

"LIMITS of the Normal and Beginnings of the Pathological in the Roentgen Picture of the Skeleton"—this descriptive title indicates the scope of the new 9th edition of the beautifully illustrated 672 page text by Köhler.[3] Beginning with the hand there are considered in turn hand, forearm, arm; shoulder, thorax, neck; skull and face; vertebrae and pelvis; lower extremity, and finally the foot and toes.

Altogether there are 1,282 illustrations; approximately 150 are diagrammatic and explanatory, the remainder beautifully reproduced roentgenograms. These are well chosen and so clearly made and reproduced, and with such fidelity, that they constitute a veritable encyclopedia of the normal structure of the skeleton and its many variations.

Throughout the volume are numerous references to the world literature, not only roentgenologic but medical, surgical, orthopedic, and pathologic. This contribution is a "working volume" that the roentgenologist and surgeon will find invaluable for constant reference.

SUMNER L. KOCH.

THE interesting book entitled *Klinische Zytologie*[4] makes profitable reading for all who deal with abnormal cytology. Although a small book it is quite comprehensive. It starts with a historical introduction which puts in proper prospective the recent developments in cytologic diagnosis. This is followed by a description of technique including the classical biopsy, needle biopsy, smears, and various puncture methods. There is a section on the morphology and general characteristics of normal and abnormal cells and a consideration of the application of qualitative and quantitive methods.

The main part of the book covers in systematic fashion the abnormal cytology of various organ systems. The gastrointestinal and respiratory tracts, body cavities, organs of locomotion, lymphatic system, liver, genitourinary organs, skin, and central nervous system are all considered in adequate de-

[1] GYNAEKOLOGISCHE STRAHLENTHERAPIE; INDIKATIONSSTELLUNG, METHODIK UND AERZTLICHE BETREUUNG. By Dr. Med. Richard Kurt Kepp. With a foreword by Prof. Dr. Heinrich Martius. Stuttgart: Georg Thieme, 1952.

[2] DISEASES OF WOMEN. By ten teachers under the direction of Frederick W. Roques. Edited by Frederick W. Roques, John Beattie, and Joseph Wrigley. 9th ed. 480 pages, 176 illustrations. $6.50. Baltimore: The Williams & Wilkins Co.; London: Edward Arnold & Co., 1953.

[3] GRENZEN DES NORMALEN UND ANFANGE DES PATHOLOGISCHEN IM ROENTGENBILDE DES SKELETTES. By Prof. Dr. A. Köhler. Revised and edited by Dozent Dr. E. A. Zimmer. 9th ed. 672 pages, 1,282 illustrations. Stuttgart: Georg Thieme Verlag, 1953.

[4] KLINISCHE ZYTOLOGIE; GRUNDRISS DER ALLGEMEINEN ZYTOLOGIE UND DER ZYTODIAGNOSTIK. By H. J. Streicher and St. Sandkuhler, with the aid of Otto A. Roth and W. Schwenkenbecher. 196 pages, 58 illustrations. DM 49.80. Stuttgart: Georg Thieme Verlag, 1953.

tail. One of the advantages of the book is that the authors discuss all available methods; for instance, in the section on bone marrow there are descriptions of biopsy methods, needle puncture methods, and smears, and each is well illustrated and described. In the section on liver, again there is a thorough consideration not only of tumors but of inflammations and degenerative diseases.

The book ends with an appendix in which the details of methods of fixation, staining, and quantitative measurement of various cellular components are given. There is also included a comprehensive bibliography.

The book is beautifully illustrated with both photomicrographs and drawings, many of which are in color. It is also well bound and clearly printed.

The book, however, gives little consideration of the clinical interpretation of the results that have been obtained by the use of cytologic methods. This was not the purpose of the authors and is only mentioned in order to give the reader an idea of the content of the book. Its greatest usefulness will be for pathologists and others who are concerned with the actual performance of these tests. Such workers will find the book of great value.

WILLIAM B. WARTMAN.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

ANATOMY OF THE BRONCHOVASCULAR SYSTEM; ITS APPLICATION TO SURGERY. By George L. Birnbaum, M.D. Foreword by Evarts A. Graham, M.D. 300 pages, 99 illustrations, and 27 plates. $15.00. Chicago: The Year Book Publishers, Inc., 1954.

THE BACTERIAL FACTOR IN TRAUMATIC SHOCK. By Jacob Fine, M.D. 82 pages, 3 illustrations. $2.75. Springfield, Ill.: Charles C Thomas, 1954.

ANESTHESIOLOGY. By Forty American Authors. Donald E. Hale, Supervising Editor, A.B., M.D., M.S., F.A.C.S., F.A.C.A. 756 pages, 149 illustrations. $15.00. Philadelphia: F. A. Davis Co. 1954.

CANCER; DIAGNOSIS, TREATMENT, AND PROGNOSIS. By Lauren V. Ackerman, M.D., and Juan A. del Regato. 2nd ed. 1201 pages, with 702 text and 23 color illustrations. $22.50. St. Louis: The C. V. Mosby Co., 1954.

LA STERILITÀ CONIUGALE. By Prof. B. Sorrentino and Prof. M. Sorrentino. 282 pages, 32 illustrations and 30 plates. Roma: Abruzzini Editore, 1954.

ERGEBNISSE DER GESAMTEN TUBERKULOSEFORSCHUNG. Edited by H. Beitzke, St. Engel, L. Heilmeyer, J. Hein, and E. Uehlinger. Vol. 12. 488 pages, 98 illustrations. DM 65. Stuttgart: Georg Thieme Verlag, 1954.

ANAIS DAS SEXTAS JORNADAS BRASILEIRAS DE OBSTETRÍCIA E GINECOLOGIA. Presidente das jornadas e redator dos anais Professor Jorge De Rezende. 793 pages, illustrated. Rio de Janeiro, 1953.

PRACTICAL FLUID THERAPY IN PEDIATRICS. By Fontaine S. Hill, M.D. 275 pages, 20 illustrations. $6.00. Philadelphia: W. B. Saunders Co., 1954.

EMETIN; SEINE WIRKSAMKEIT AUF SCHWERE CHIRURGISCHE INFEKTE. By Prof. Dr. Eduard Melchoir. 132 pages, 57 illustrations. DM 11.50. Stuttgart: Ferdinand Enke Verlag, 1954.

MONOGRAPHS IN BIOLOGY AND MEDICINE. Vol. 3. DIENCEPHALON; AUTONOMIC AND EXTRAPYRAMIDAL FUNCTIONS. By Walter Rudolf Hess, M.D. 79 pages, 33 illustrations. $4.00. New York: Grune & Stratton, 1954.

PRACTICAL OBSTETRICS. By Bruce T. Mayes, M.V.O., M.B., B.S. (Sydney), F.R.C.S. (Edin.), F.R.A.C.S., F.R.C.O.G. Foreword by John A. Stallworthy, M.A. (Oxon.), F.R.C.S. (Eng.), F.R.C.O.G. 500 pages, 181 illustrations. Sydney; London: Angus and Robertson, 1954.

PEARCE GOULD'S ELEMENTS OF SURGICAL DIAGNOSIS. 10th ed., revised by Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., M.Ch., D.Sc., F.R.C.S., F.A.C.S. 586 pages, 19 plates. $7.50. New York: Paul B. Hoeber, Inc., Med. Book Dept. of Harper & Bros., 1954.

STONE IN THE URINARY TRACT. By H. P. Winsbury-White, M.B., Ch.B. Ed., F.R.C.S. Ed., F.R.C.S. Eng. 2nd ed. 328 pages, 144 illustrations. $16.00. London: Butterworth & Co., Ltd.; St. Louis: The C. V. Mosby Co., 1954.

ARCHIV UND ATLAS; DER NORMALEN UND PATHOLOGISCHEN ANATOMIE IN TYPISCHEN ROENTGENBILDERN. FUNKTIONELLE ROENTGENDIAGNOSTIK DER HALSWIRBELSAEULE. By Dr. C. Buetti-Bäuml. 160 pages, 154 illustrations. DM 42. Stuttgart: Georg Thieme Verlag, 1954.

STÉRILITÉ; FEMININE-MASCULINE. By P. Funck-Brentano, H. Bayle, and R. Palmer. 80 pages, 14 illustrations. 400 fr. Paris: Masson et Cie, 1954.

CANCER; LES DIAGNOSTICS CYTOLOGIQUES LE CANCER DU SEIN. By J. Delarue, J. Paillas, L. Orcel, A. Sicard, L. Leger, P. Gibert, and M. Perrault. 122 pages, 18 illustrations. 760 fr. Paris: Masson et Cie, 1954.

CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

FRANK GLENN, New York, *President*
ALFRED BLALOCK, Baltimore, *President-Elect*

PRELIMINARY PLANS FOR 40TH CLINICAL CONGRESS CONVENTION HALL, ATLANTIC CITY, NEW JERSEY NOVEMBER 15 TO 19, 1954

THE program of the 40th Clinical Congress of the American College of Surgeons continues to grow in scope. Again this year new features have been added, making the program ever more useful and meeting the College ideal of unceasing postgraduate education of the surgeon.

Recent issues of SURGERY, GYNECOLOGY AND OBSTETRICS have already called attention to this most popular and widely instructive meeting of surgeons: the July issue indicated the broad outlines of the program; the August issue presented some details of the surgical specialty sessions. Additional information on postgraduate courses, and description of other scientific meetings are included here. The October issue will carry an almost complete program.

OFFICIAL MEETINGS

Two official evening sessions will be held. At the opening evening meeting on Monday, Dr. Robert H. Kennedy will give the Oration on Trauma, and Dr. Alan Gregg, Vice President, the Rockefeller Foundation, will give the Martin Memorial Lecture, speaking on "Horizons at Half Century."

The Annual Meeting of Fellows is scheduled for Thursday afternoon. On Friday evening the Convocation will be held, new officers will be inaugurated, and honorary Fellowships conferred. Alfred Blalock, incoming president of the College, will deliver the Presidential Address at this meeting.

Tuesday and Wednesday evenings will be held open for special group meetings. On Thursday evening the Motion Picture Symposium will be held.

POSTGRADUATE COURSES

The number of Postgraduate Courses offered at this forthcoming Congress has been increased to eight, including three in the surgical specialties: Gynecology and Obstetrics, Orthopedic Surgery, and Thoracic Surgery. Each course occupies the forenoons of Monday, Tuesday, Wednesday, and Thursday of the Congress week. Sessions will run from 8:30 to 11:30 a.m. Registration for these popular courses will be limited, so it is important to make reservations in advance. Official registration forms must be obtained from the American College of Surgeons, 40 East Erie Street, Chicago 11, Illinois.

The following list shows the subtopics for the sessions composing each of the Postgraduate Courses:

Cardiovascular Surgery. JOHN H. GIBBON, JR., Chairman.

Monday:
Portal Hypertension and Bleeding Esophageal Varices.
Surgical Treatment of Acquired Cardiac Diseases.

Tuesday:
Congenital Anomalies of the Heart and Great Vessels.

Wednesday:
Cardiac Septal Defects, Transpositions, Hypothermia and Extracorporeal Blood Circuits.

Thursday:
Aneurysms and Arteriosclerosis.

Preoperative and Postoperative Care. JONATHAN E. RHOADS, Chairman.

Monday:
Preparation of Patients for Various Operative Procedures.

Tuesday:
Special Problems in the Surgical Care of Patients with Biliary Tract Disease.

Wednesday:
Postoperative Complications, Prophylaxis and Treatment.

Thursday:
Special Problems in Preoperative and Postoperative Care.

Surgery of the Lower Esophagus, Stomach and Duodenum. REGINALD H. SMITHWICK, Chairman.

Monday:
Lesions of the Lower Esophagus.
Tuesday:
Gastric Neoplasms.
Wednesday:
Gastric Ulcer and the Ulcer-Cancer Problem.
Thursday:
Duodenal Ulcer.

Diseases of the Liver, Biliary Tract and Pancreas. NATHAN A. WOMACK, Chairman.

Monday:
Hepatic Circulation and Hepatic Anomalies.
Liver Dysfunction.
Cirrhosis of the Liver.
Portal Hypertension.
Tuesday:
The Jaundiced Patient, Cancer, Trauma and Bile Duct Repair.
Wednesday:
Cholecystitis, Gallstones, and Persistence of Symptoms Following Cholecystectomy.
Thursday:
Pancreas.

Combined Injuries to the Extremities. HARRISON L. MCLAUGHLIN and HAROLD A. ZINTEL, Co-Chairmen.

Monday:
Hand.
Tuesday:
Arm and Shoulder.
Wednesday:
Hip and Pelvis.
Thursday:
Knee and Leg.

For the Surgical Specialties:

Gynecology and Obstetrics—Surgical Procedures in Obstetrics and Gynecology; Indications, Anesthesia, Technique. THADDEUS L. MONTGOMERY, Chairman.

Monday:
Obstetrical Operations and Delivery.
Tuesday:
Vagino-Plastic Procedures.
Wednesday:
Hysterectomy, Myomectomy.
Thursday:
Tubo-Ovarian Surgery.

Orthopedic Surgery—Lower Extremity Amputations and Prostheses. HARRY D. MORRIS, Chairman.

Monday:
Open Amputation—Indications, Technique, After Care and Plastic Revision.
Amputations About the Foot and Ankle.
Tuesday:
Amputations Below the Knee.
Amputations Above the Knee.
Wednesday:
Amputations About the Hip.
Special Amputation Problems of Surgical Technique and Fitting in Children.
Thursday:
Special Amputation Problems in Patients with Peripheral Vascular Disease.
Rehabilitation as Applied to the Lower Extremity Amputee.

Thoracic Surgery—The Surgical Aspects of Pulmonary Disease. RICHARD H. OVERHOLT, Chairman.

Monday:
A Symposium on Preoperative Preparation, Anesthesia and Postoperative Management.
Tuesday:
The Surgical Management of Pulmonary Tuberculosis.
Wednesday:
The Management of Diseases other than Tuberculosis or Neoplasm.
Thursday:
Surgical Problems of Pulmonary Neoplasms.

CLINICOPATHOLOGY CONFERENCES

Two Clinicopathology Conferences will be held at this Congress, the first on Monday, from 1:30 to 3:00 p.m. Robert C. Horn, Jr., Philadelphia, will be moderator. His collaborators will be William T. Fitts, Jr., Richard A. Kern, George P. Rosemond, and Francis C. Wood—all of Philadelphia.

The second conference will be held on Wednesday, also from 1:30 to 3 p.m. John M. Pearce, New York, will act as moderator. His collaborators will be Claude E. Forkner, New York, Emile Holman, San Francisco, and Richard Warren, Brookline.

SURGICAL FORUM

Representatives of five special fields of surgery have been added to the membership of the Forum Committee. Additional Forum sessions are being scheduled this year, and seven sessions will be devoted exclusively to special fields of surgery, including anesthesiology.

The members of the Surgical Forum Committee, after their meeting at which papers were selected for the 1954 Forum sessions, were unanimous in the opinion that an unusually fine group of research reports had been received for this year's Congress.

WHAT'S NEW IN SURGERY?

An innovation this year will be a general session under this title on Friday morning, 9 a.m. to 12 noon, under the auspices of the Surgical Forum Committee. At this session, a number of the presiding officers of Forum sessions, including the surgical specialties, will summarize the "highlights" of research in their respective fields, conducted during the current year and reported at the Forum sessions.

MOTION PICTURES—CINÉ CLINICS

The scope of the motion picture program has been expanded and presents some new features. Ciné Clinics will be held Tuesday through Friday morning. In addition to the personal appearance of the surgeon for the commentary, while the film is being shown, there will be a unique type of introduction of the author on the screen. A new type of Ciné Panel Discussion will be carried out for three films on a related subject. The regular motion picture program will be conducted in the manner of a symposium, i.e. Surgery of the Intestines, Head and Neck Surgery, Surgery of the Esophagus and Stomach, and Surgery of the Liver, Biliary Tract, and Pancreas. In addition there will be periods devoted to surgical specialties: Obstetrics, Gynecology, Urology, Plastic Surgery, Orthopedic Surgery, Thoracic Surgery, and Cardiovascular Surgery. A special motion picture program is planned for Thursday evening. Authors of films will be present to provide commentary or discussion.

ADVANCE REGISTRATIONS

All official registration forms—advance registration, postgraduate courses, transportation, and hotel accommodations—must be obtained from College headquarters in Chicago. It is advisable to register well in advance to insure obtaining your first choice in courses and accommodations.

No registration fee is charged Fellows whose dues are paid as of December 31, 1953; no registration fee is required of Initiates, Junior Candidates, or Surgical Residents whose applications are accompanied by a letter of identification from the chief surgeon or hospital administrator. Non-Fellows will pay $20.00, and members of Federal Services $10.00.